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The
PROCEEDINGS
of
The American Association
for the Study and Control of
Rheumatic Diseases

SECOND ANNUAL MEETING AND FOURTH
CONFERENCE HELD AT

Atlantic City, N. J., JUNE 10, 1935

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1 JUN 1938

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VICE-PRESIDENT.....DR. RUSSELL L. HADEN
SECRETARY.....DR. LORING T. SWAIM

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INTRODUCTORY REMARKS

PRESIDENT'S ADDRESS

ERNEST E. IRONS, M.D., CHICAGO, ILL.

WE TAKE pleasure in welcoming all to this Second Annual Meeting of the American Association for the Study of Rheumatic Diseases.

The contributions to last year's program were extremely interesting and valuable. They have been collected, printed and distributed to members and others. The papers on this program give promise of being equally important and profitable. It is the plan of your Executive Committee to publish these Proceedings.

You will note by the program that this morning session is devoted to chronic arthritis, and the afternoon to rheumatic fever. We are specially gratified by the excellence of the program prepared by the Committee for this afternoon.

It is evident that the study of the complex system of variables presented in arthritis must be conducted by a consideration of each one or of each group of these variables and so of necessity studies of arthritis are concerned with one or another of the causative agents or contributing elements in the disease. Such studies are frequently unrelated, except for the fact that they are part of the investigations necessary to the ultimate understanding of the larger whole.

Even before the results of these separate studies are completely correlated, they are seen to follow certain general lines. It is to these current trends of thought in arthritis that I wish to refer. Most of these comments are so familiar that reference to them almost calls for an apology. Nevertheless a restatement of facts is sometimes profitable.

The concept of chronic arthritis as a general disease rather than one of the joints alone is steadily gaining ground. It is generally conceded that there are many initiating and contributing causes in chronic arthritis. These include infection, trauma, age, heredity, disturbances of vascular supply or of general and local nutrition, and metabolic and glandular dysfunction. Various combinations of these causes and conditions in individual patients result in varying clinical pictures, whose common factor is involvement of joints and structures attached to the bony skeleton. No one single cause or condition is common to all cases of arthritis.

It seems generally agreed that (no matter how great the disagreement as to the original cause of first symptoms) the division of chronic arthritis into two great groups, the atrophic (rheumatoid) and hypertrophic (osteo-) arthri-

tis, is extremely serviceable. One of the chief values of this classification rests on the fact that it takes into consideration the previous reactions of the tissues of the patient, and so prophetically indicates the kind of changes he is likely to suffer in the future, and therefore the measures which should be taken to meet and modify the disability which threatens him.

There still is disagreement as to whether these two great groups represent separate clinical entities. Some hold that hypertrophic arthritis is an entity, no matter what may be concluded as to the atrophic forms, and still others are firm in support of the clinical entity of the atrophic group. It seems to be generally agreed however that evidences of the effects of infection are much more clear in atrophic, than in hypertrophic arthritis.

Is it not possible that the disease process in chronic arthritis assumes this or that course with the production of one or another type of arthritis by reason of the kind, age, and resistance of tissues of the patient whose joints have suffered an initial insult? It may even be argued that the same insult which initiates in one person an atrophic arthritis might, if received by a person whose tissues were less vulnerable, have caused no more than a temporary disability. In this connection consider the variety of types of arthritis which may follow gonococcal infection, from an acute temporary and quickly healing arthritis to the chronic forms indistinguishable from "atrophic arthritis," or again from spondylitis ankylopoetica of the British classification.

The influence of heredity seems as clear in atrophic arthritis occurring in grandmother, mother, and daughter, as in the family incidence of early hypertension. Racial, familial, and individual peculiarities in connective tissue response to injury as illustrated by the variable formation of keloid in surgical scars, and the varying rapidity and extent of callus formation after fractures, indicate the wide range of tissue response to trauma. The same factors may influence the course of the healing of tissues of joints.

Other similar comments might be offered with respect to the progress of disease in the joints themselves, as well as other perhaps obvious observations on the reactions of the body as a whole to infection, trauma, and local and general derangements of nutrition. While some of these questions are controversial, they serve to reemphasize the importance to the student of arthritis of the conception of arthritis as a disease of the entire body.

Another phase of the problem of arthritis concerns the use of physiotherapeutic measures. In hospital centers where the study of chronic arthritis is particularly advanced, equipment of many sorts for hydrotherapy and physiotherapy has been installed. Some of this is of undoubted value; some suggests an associated and undesirable commercialism. Much of it is expensive, and in the form offered is not practicable for home treatment.

While many patients are treated in larger centers, and many more come for diagnosis and the outlining of a program to be carried out later, the majority of sufferers from chronic arthritis must be treated entirely in their own communities by their family physicians. One of the greatest services to these patients will be the formulation of suitable methods of treatment in

the home by the use of equipment improvised at very small expense. A fuller knowledge by physicians of what can be done, and how it should be done, will benefit patients and at the same time lessen the excuse for the existence of pseudomedical cults.

Before leaving the subject of physical therapy, I wish to suggest the possible good results to be obtained by the application of negative and positive pressure to the joints of the extremities by means of the Paevex or similar machines now used in the treatment of vascular obstruction and threatened gangrene of the extremities.

Certain cases of atrophic arthritis with impaired nutrition and shiny atrophic skin will be called to mind as possibly suitable for this type of treatment. In a few cases selected for trial, results seem to warrant further experimental employment of this treatment.

Another problem concerns the establishment of hospitals for the treatment of arthritis where study and treatment may be highly developed by well-qualified investigators in bacteriologic, metabolic, and orthopedic aspects, skilled in the application of knowledge to the needs of each individual patient.

Such clinics already exist at certain medical centers and will be most successful if developed as a part of a large general clinic. Clinics for arthritis alone, established apart from other medical projects, may offer superior custodial advantages for those patients whose hospital care must be prolonged over many months. They are likely, however, to suffer from lack of stimulus from other departments of a general clinic. Undoubtedly there may be instances in which a separate institution for the care of arthritis would do better work than a general hospital by reason of the centering of effort on one subject under the inspiring leadership of some one man.

On the other hand, the relations of arthritis to other diseases might thus tend to be minimized, and it would seem that the chances of reversion from active centers of study to institutions for custodial care would be greater if the arthritis hospital were detached than if it were closely associated with a general medical clinic.

ACCELERATING FACTORS IN CHRONIC HYPERTROPHIC ARTHRITIS (OSTEOARTHRITIS)

RUSSELL L. HADEN, M.D., AND WIRT A. WARREN, M.D., CLEVELAND, OHIO

HYPERTROPHY of bone may develop secondarily around a joint in almost any type of chronic arthritis. Such a change is common in the late stage of chronic atrophic (rheumatoid) arthritis. Abnormal mechanical stress on a joint otherwise normal also may result in a hypertrophy of subchondral bone as in scoliosis. Primary hypertrophic arthritis (osteoarthritis), however, represents a degeneration of joint cartilage and proliferation of subchondral bone incident to physiologic aging and the wear and tear of continued use. The fundamental pathologic process is a fibrillation of cartilage, softening and erosion of the joint surface, and a loss of the protective power normally afforded by the cartilage. Any factor which adds to the physical stress of the joint will hasten erosion of cartilage after softening has begun. The more important physical factors are occupation, static deformities, and trauma. Such factors, however, are not etiologically related to the primary degeneration in the cartilage.

If degeneration of cartilage in primary hypertrophic arthritis (osteoarthritis) represents an aging process, we should not think of etiologic factors here since old age is a normal stage in the life of all body tissues. Old age, however, becomes a disease if it comes prematurely as a result of the shortening of the normal span of life by acceleration of the chemical processes on which life depends. There are certain physiologic criteria corresponding to different chronologic ages. The physiologic and chronologic ages may be dissociated, more commonly with the physiologic exceeding the chronologic age. Studies show that every person will have some degree of degeneration of cartilage and hypertrophy of bone if he lives long enough, just as he will have gray hair. In clinical work, our problem is the frequent development of such changes prematurely or a physiologic age exceeding the chronologic age. Numerous factors may contribute to or accelerate physiologic aging. The problem is much the same as premature graying of hair and often runs parallel with it. If one enumerates the factors which may cause gray hair prematurely, he has in mind the factors which lead to degeneration of joint cartilage out of proportion to age.

We have analyzed fifty consecutive cases (8 males, 42 females) of chronic hypertrophic arthritis in relation to the following accelerating factors: (1) Heredity, (2) worry and emotional stress resulting in lack of rest, (3) hard physical labor, (4) illness of general nature from any cause, (5) focal infection, (6) gastrointestinal disorders with disturbance in alimentation, (7) metabolic abnormality, especially lowered metabolic rate, (8) endocrine imbalance, and (9) disturbed circulation, especially by hypertension and arteriosclerosis. Each patient came in primarily because of joint symptoms and was found to have an active arthritis which was classified as degenerative in type. We have

included no cases in which degenerative arthritis was an incidental finding. The method of study after a careful history and complete physical examination has been as follows: (1) Roentgenogram of a typical joint; (2) routine study of blood for anemia and of urine for any abnormality; (3) search for a focus of infection—teeth, tonsils, sinuses, prostate and cervix; (4) complete study of gastrointestinal tract (gallbladder, size and shape of colon, gastric acidity); (5) sedimentation rate of erythrocytes; (6) blood chemical study (glucose tolerance, uric acid); and (7) basal metabolic rate.

A few patients did not have every examination. The glucose tolerance test was the one most frequently omitted. The group of 50 includes 8 males and 42 females. The average age of the males was fifty-two and of the females, fifty-one. The age range of the males was from thirty-nine to fifty-eight and of the females, from thirty-four to sixty-nine years. The average duration of symptoms in the males was seven plus years and in the females four plus. Certain important factors are most difficult to evaluate statistically. Heredity is a most important factor, but a family history of arthritis is so unreliable that no figures were attempted for this factor. The condition of any tissue at any time necessarily depends on how good it was to start with, so heredity is fundamental. It is also difficult to evaluate worry and emotional stress as well as physical labor, but exhaustion and fatigability were prominent symptoms, however, in addition to the joint disability.

Only two patients gave a history of a serious general illness within the preceding five years. Most were remarkably well except for the exhaustion and joint disability, although a few were of the chronic invalid type. When the age group is taken into consideration, a relatively small proportion (42 per cent) had evidence of focal infection. Thirty-two per cent showed chronic tonsillar infection, 20 per cent had some dental infection, and 10 per cent had other foci such as chronic prostatitis.

The incidence of overweight is striking. Sixty-two per cent of the group weighed more than normal for their age and height. The average percentage of overweight was twenty-five pounds. This increased weight adds to the physical strain of weight bearing and indicates a metabolic overstrain as well, since no patient who is gaining weight is in metabolic balance.

The tendency to overweight is closely correlated with a lowered rate of metabolism. Eighty-four per cent of the group had a basal metabolic rate below the normal average for their age. The average decrease below normal was 15 per cent. The rates in a small number were above normal (16 per cent) showing only a slight increase (5 per cent). Most patients had only a single determination, and since the rate is often higher than it should be on the first test, it is probable that a still larger number actually had a low metabolic rate. Since the metabolic rate records the speed at which the tissues are working, these results indicate a marked slowing of chemical activity. Old age after all is only a gradual slowing up of metabolic processes, so the characteristic low metabolic rate is the best indication of premature aging in chronic degenerative (hypertrophic) arthritis (osteoarthritis).

The sedimentation rate of the erythrocytes was within normal limits in 80 per cent of the cases and very little elevated when beyond the normal range. Not infrequently, an increased suspension stability was observed associated with a rate lower than the average normal. This only verifies the observations of other workers. Anemia was a rare finding. Only 4 per cent of the total had a hemoglobin below 75 per cent (11.5 gm. per 100 c.c.). The uric acid constantly tended to be elevated although not markedly so. Fifty-five per cent had a uric acid of more than 2 mg. (but not markedly so) which is above our average with the method used. The single blood sugar determinations were seldom above normal, but 22 per cent of the group showed a diminished tolerance or a frankly diabetic curve with a glucose tolerance test.

In the study of the gastrointestinal tract, 60 per cent were constipated. It is difficult to evaluate the importance of this finding when it is so common. No attempt was made to procure a dietary history since a dependable one is so difficult to obtain. Overeating, both in amounts of food and in starchy foods with low intake of protective foods, often seemed evident. Twelve per cent had achlorhydria, 20 per cent hypochlorhydria and 28 per cent hyperchlorhydria, so the gastric acidity seems of little importance. Gallstones were found in 14 per cent and a nonfunctioning gallbladder by the Graham-Cole test in 80 per cent. The colon was atonic and redundant in 28 per cent. This finding was frequently observed to a high degree.

The association of chronic degenerative arthritis with the menopause has long been emphasized. Only 19 per cent of the 42 females were still menstruating. The onset of symptoms had been coincident with the menopause in 36 per cent, and after the menopause in 45 per cent. No other defects in endocrine activity were discovered except the frequent finding of dry hair and skin and brittle nails, suggestive of hypothyroidism in the patients with hypometabolism.

Vascular disease is also difficult to evaluate statistically, although the arteries are frequently well outlined by calcareous deposits in radiographs of the joints. This is often much out of proportion to what we consider normal in relation to chronologic age. Twenty-four per cent of the females had a systolic blood pressure over 140. None of the males had a systolic pressure over 145. The frequent observation of calcareous deposits in arteries, the common finding of arterial hypertension, and the well-known gradual decrease in capillary bed with age, all emphasize the circulatory factor in chronic hypertrophic arthritis.

DISCUSSION

The results of this study only emphasize again certain salient facts concerning degenerative (hypertrophic) arthritis (osteoarthritis) which are already known to most students of chronic arthritis. Infection evidently plays a minimal part in the acceleration of the joint disease. The most significant findings are the tendency to overweight and the great frequency of a low metabolic rate. The patients are nearly all within the age period when degeneration of tissues begins or is prominent. The disease was always slowly progressive, so symptoms had been present for several years before medical aid was sought.

We have been much impressed with the constancy with which the patients complained of exhaustion and the frequent disproportion between chronologic and physiologic age. It seemed evident frequently that the chemical activity of body tissues must have been at low ebb for years in many patients. Normal old age may be thought of as a gradual slowing up of metabolic activity. In the group of conditions so commonly associated with this disease are arteriosclerosis and hypertension, obesity, diabetes, and chronic hypertrophic arthritis. We have a premature slowing of metabolism characteristically in degenerative arthritis. Patients are now being observed who are known to have had a low metabolic rate for several years before the signs of degenerative arthritis were evident. The obesity is commonly due to a low rate of metabolism. It seems possible that toxic substances are formed when the combustion is impaired, although it is equally possible that the important factor may be impaired nutrition of the cartilage secondary to the low metabolic rate or impaired circulation. Unfortunately, little is known about intermediate products of metabolism which may injure cartilage. Uric acid and homogentisic acid are two substances known to deposit in and damage joint surfaces. There must be others.

After the degeneration of joint cartilage has taken place, nothing can be done to replace it. Measures which increase tissue activity will do much to slow the progress of the disease. If accelerating factors are looked for and eliminated, much can be done to decrease the incidence of serious or disabling chronic hypertrophic arthritis (osteoarthritis).

SUMMARY

Fifty consecutive patients with chronic hypertrophic arthritis (osteoarthritis) have been studied for factors which influence the development or progress of the disease.

Women predominate in the series—five to one.

The degeneration of cartilage characteristic of the disease is a manifestation of the physiologic aging of tissues.

Increased physical strain will hasten the erosion of the degenerated cartilage.

Certain factors will accelerate the primary changes in the cartilage.

The more important accelerating factors are: obesity, lowered metabolic rate, disturbed alimentation, endocrine dysfunction, and circulatory inadequacy.

DISCUSSION

DR. WALTER A. BAUER, BOSTON.—For the past six years, Dr. G. A. Bennett and I have been interested in this type of joint disease. To obtain an accurate picture of supposedly normal joints at various ages, we collected a series of knee joints from normal individuals who so far as we could determine had never had symptoms or signs of previous joint disease. At least six knee joints, representing each decade of life from the first to the ninth, were obtained at necropsy. With each succeeding decade in life beyond the second, the knee joints showed increasing pathologic changes, degenerative in nature and indistinguishable from those characteristic of chronic degenerative arthritis. The frequency and extent of these changes increased so rapidly from the second decade on that by the fifth decade of life all joints showed the characteristic changes of chronic degenerative arthritis.

In any discussion pertaining to the cause of degenerative arthritis, one must appreciate two facts: (1) That the pathology in this type of joint disease is primarily a degeneration

of articular cartilage, other changes being secondary to this process; (2) that, except for its limited perichondrial blood supply, articular cartilage is an avascular structure. The fact that articular cartilage has a more limited source of nourishment than most other body tissues is probably sufficient reason for its having a low metabolism and a limited ability to repair. If a tissue has a limited ability to repair, one would expect to find more evidence of the changes resulting from the wear and tear of daily use and increasing age than in other tissues where such limitations of repair do not exist. That such is the case with articular cartilage would seem to be borne out by our studies which with other experimental and clinical observations have led us to conclude that degenerative arthritis is primarily, if not solely, the result of wear and tear, with changes resulting from long-continued use of a relatively avascular structure which has a limited ability to repair. The greater the wear and tear, unusual use and repeated traumas a joint is subjected to, the earlier these changes will appear.

We agree with Dr. Haden that some persons inherit better cartilage than others. Those who inherit poor articular cartilage will develop this type of joint change, at a much earlier age. That such is true seems often evident from the family history of such patients.

There are often other factors present which will accelerate this degenerative process. The known factors operative in the case of the knee joint include obesity, knock knees, bowlegs, flat feet, imperfectly set fractures, faulty body mechanics, etc. Examples of such accelerating factors are constantly seen in the clinic. Loss of pain sense, as in tabes dorsalis, syringomyelia, and leprosy, allows such changes to take place more rapidly unbeknown to the patient.

Dr. Haden suggests the existence of other accelerating factors, particularly of chemical origin. To date we have no proof of their existence. However, we do occasionally see an individual who develops obvious degenerative joint disease at an earlier age than normal without a satisfactory explanation such as poor inheritance or any obvious accelerating factor. We must study this small group more carefully to determine what factors are at work which could impair the articular cartilage and thus allow for the early development of such joint changes.

DR. M. H. DAWSON, NEW YORK, N. Y.—Dr. Haden has presented us with interesting information on certain metabolic changes which occur in degenerative arthritis. Has he studied the corresponding changes in other degenerative diseases such as arteriosclerosis? From his data it would appear that he is comparing changes observed in degenerative arthritis with findings in normal individuals. Before the significance of his observations can be evaluated properly it will be necessary to carry out corresponding studies in other chronic degenerative diseases.

DR. J. A. KEY, ST. LOUIS, MO.—I wonder about controls. I was impressed with the fact that uric acid determinations were included in the charts. Long before I was born people talked about the relationship of uric acid to arthritis of this type. Sometimes after these old theories are given up some one comes along and finds a basis for them. Some one should study some controls to see if there is basis for the uric acid theory.

DR. RUSSELL L. HADEN, CLEVELAND, O. (Closing).—May I answer Dr. Dawson's question by asking him one? What makes arteriosclerosis? I do not think these findings are limited to degenerative arthritis, since they are found with equal frequency in other degenerative diseases. I cannot give figures for a control group. Heredity, an important factor, is something we can do nothing about. In the group reported here we have tried to find something influencing the development of degenerative arthritis, and to see if we cannot correct the influencing factors. Such an approach is important in all degenerative diseases. Arteriosclerosis, hypertension, obesity, diminished carbohydrate tolerance, and degenerative arthritis frequently occur together. I think we will eventually find chemical changes responsible for all of them.

BACTERIOLOGIC AND IMMUNOLOGIC STUDIES IN ARTHRITIS*

I. RESULTS OF BLOOD CULTURES IN DIFFERENT FORMS OF ARTHRITIS

CURRIER MCEWEN, M.D., R. C. ALEXANDER, M.A., AND JOSEPH J. BUNIM, M.D.,
NEW YORK, N. Y.

THE importance of correct classification of cases in studies of joint disease is obvious, but especially so in attempts to evaluate the efficacy of different forms of treatment. Although great advances have been made during the past thirty years in the differentiation of various types of these diseases, much remains to be accomplished; for, while typical examples of rheumatic polyarthritis, rheumatoid arthritis, osteoarthritis, gout, gonococcal arthritis, and others are now easily recognized by clinical and simple laboratory means, there are many atypical examples which can be placed in their proper categories only after long observation or never. The work here reported is part of a general study of methods which might prove of value in the differential diagnosis of such cases.

During recent years there has been a revival of interest in bacteriologic and serologic tests as applied to the study of arthritis. This has come about largely because of three developments: (1) the success of some investigators in obtaining positive blood cultures in certain types, (2) the accumulation of indirect evidence linking hemolytic streptococci with rheumatic fever and rheumatoid arthritis, and (3) the development of new serologic tests for the recognition of hemolytic streptococcal infections. The purpose of this and the following paper is to report results obtained in applying certain of these bacteriologic and serologic methods to the study of a group of patients with various types of arthritis; this first paper is concerned with results of blood cultures.

In view of the availability of comprehensive reviews^{1, 2} covering reports of blood cultures in rheumatic fever and chronic arthritis, no detailed historical résumé is required here. In Table I, however, are summarized results obtained in representative investigations since the adoption of Schottmüller's³ classification of streptococci according to their effect on blood. This list makes no pretense at completeness but serves to illustrate the often emphasized lack of uniformity in results obtained by different workers. Chief interest, from the point of view of the present study, centers in the reports of Cecil, Nicholls and Stainsby^{11, 12, 13} because of their high percentages of positive cultures and the uniformity with which they obtained green streptococci from patients with rheumatic fever and hemolytic streptococci from those with rheumatoid arthritis.

MATERIAL

Blood cultures were included in the routine study of all patients with joint disease entering the wards and Arthritis Clinic of the Third (New York Uni-

*From the Department of Medicine, New York University College of Medicine and the Third (New York University) Medical Division of Bellevue Hospital.

TABLE I

SUMMARY OF RESULTS OF BLOOD CULTURES OBTAINED BY VARIOUS INVESTIGATORS

AUTHORS AND DISEASES STUDIED	NUMBER OF PA- TIENTS	PA- TIENTS POSI- TIVE	PATIENTS YIELDING				REMARKS
			STREPTOCOCCI			DIPH- THEROID BACILLI	
			HEMO- LYTIC	GREEN	INDIF- FER- ENT		
		PER CENT*	PER CENT*	PER CENT*	PER CENT*	PER CENT*	
1917 Moon and Edwards ⁴ Acute arthritis	40	40.0	2.5	32.5		5.0	2% staph. and 5% <i>B. mucosus</i>
Chronic arthritis	83	26.0		22.0		4.0	4% <i>B. mucosus</i>
1917 Swift and Kinsella ⁵ Rheumatic polyarthritis	58	12.0		12.0			
1920 Richards ⁶ Chronic arthritis—types?	104	13.0		13.0			
1924 Freund and Berger ⁷ Rheumatic polyarthritis	23	65.0	4.0	65.0			4% mixed green and hemolytic
Miscellaneous diseases	35	14.0	6.0	14.0			6% mixed green and hemolytic
1927 Hadjopoulos and Burbank ⁸ Chronic arthritis—types?	145	17.0	6.0	4.0	1.0	5.0	1% strep. (variety?) 1% mixed hemo- lytic and green 3% staphylococci
1928 Lazarus-Barlow ⁹ Rheumatic fever	33	0.0					
1928 Suranyi and Forro ¹⁰ Polyarthritis—type?	25	68.0		68.0			
1929 Cecil, Nicholls, and Stains- by ¹¹⁻¹³ Rheumatoid arthritis	78	70.0	51.0	8.0	3.0	5.0	3% <i>Micrococcus</i> <i>zymogenes</i>
Rheumatic fever	60	60.0	1.5	55.0	1.5	1.5	
Osteoarthritis	23	0.0					
Normal controls	20	0.0					2% strep.—vari- ety?
Pathologic controls	61	7.0		5.0			
1929 Nye and Seegal ¹⁴ Rheumatic fever	25	0.0					
1929 Rosenow ¹⁵ Chronic infectious arthritis	19	37.0		37.0			
1930 Jordan and Boland ¹⁶ Acute polyarthritis	32	0.0	No streptococci				31% gram-neg.— minute bacilli
Miscellaneous controls	16	0.0	No streptococci				No gram-neg.— minute bacilli
1930 Margolis and Dorsey ¹⁷ Chronic infectious arthritis	89	10.0		5.5	3.5	2.0	Both indif. strep. and diphtheroids in 1 culture.

*Percentages are calculated from figures of authors quoted to make data in this table comparable with those in Table II. Most of the percentages are merely approximate.

†These figures designate numbers and percentages of cultures rather than of patients.

TABLE I—CONT'D

AUTHORS AND DISEASES STUDIED	NUMBER OF PA- TIENTS	PA- TIENTS POSI- TIVE	PATIENTS YIELDING				REMARKS
			STREPTOCOCCI				
			HEMO- LYTIC	GREEN	INDIF- FER- ENT	DIPH- THEROID BACILLI	
		PER CENT*	PER CENT*	PER CENT*	PER CENT*		
1930							
Nye and Waxelbaum ¹⁸							
Rheumatic fever	12	0.0					
Acute infectious arthritis	11	0.0					
Chronic infectious arthritis	10	10.0				10.0	Occasional staphs. in most groups
Osteoarthritis	8	0.0					
Gonococcal arthritis	3	0.0					
Miscellaneous diseases	19	0.0					
1931							
Coburn ¹⁹							
Rheumatic fever	84	15.5	2.5	7.0		6.0	2% more gave staphylococci
1931							
Bernhardt and Hench ²⁰							
Chronic infectious arthritis	20	5.0				5.0	20% more gave staphylococci
1931							
Gray and Gowen ^{21, 22}							
Rheumatic fever	13	38.0		38.0		"Small per cent"	
Rheumatoid arthritis	200	48.0	48.0	"Similar to Cecil's typical strains"			
Osteoarthritis	79	0.0					
1931							
Weil ²³							
Rheumatic polyarthritis	35	8.0		6.0			2% streptococci (variety?)
1932							
Ashworth ²⁴			28.2 streptococci "similar to Cecil's typical strains." 9.4 diplococci				Staph. contami- nants
Rheumatoid arthritis	138	40.6					
1932							
Cooley ²⁵							Occasional staph- ylococci in both groups
Rheumatic fever	25	0.0					
Nonfebrile controls	10	0.0					
1932							
Dawson, Olmstead & Boots ²⁶							
Rheumatoid arthritis	204†	8.5†		1.0†	0.5†	6.0†	1% gram-pos. cocci (variety?)
Normal controls	31†	3.0†				3.0†	
1932							
Lichtman and Gross ²⁷							1.5% streptococci (variety?)
Rheumatic fever	188	10.5	0.5	2.0	6.0	}	0.5% pneumococ- cus
Rheumatoid arthritis	48	8.0	2.0		4.0		2% streptococci (variety?)
Miscellaneous diseases	220	7.5	20.0	3.5	3.0		1% streptococci (variety?)
1932							
Steinfeld ²⁸							
Chronic arthritis—type?	10	20.0					

TABLE I—CONT'D

AUTHORS AND DISEASES STUDIED	NUMBER OF PA-TIENTS	PA-TIENTS POSITIVE	PATIENTS YIELDING				REMARKS
			STREPTOCOCCI			DIPH-THEROID BACILLI	
			HEMO-LYTIC	GREEN	INDIF-FER-ENT		
		PER CENT*	PER CENT*	PER CENT*	PER CENT*	PER CENT*	
1933 Callow ²⁹ Rheumatic fever	367†	53.0†	0.3†	18.0†	3.0†	See re-marks	4% mixed types and 27% pleo-morphic bacilli
Normal controls	43†	14.0†		„			14% pleomorphic bacilli
1933 Wilson and Edmond ³⁰ Rheumatic fever	236†	22.0†		4.0†	7.0†	See re-marks	11% pleomorphic bacilli
Normal and pathologic controls	153†	29.0†		8.0†	4.0†		17%† pleomorphic bacilli

versity) Medical Division of Bellevue Hospital and the Arthritis Clinic of the New York University College of Medicine Clinic over the period October, 1932, to August, 1935. On discharge from the wards all patients were referred to the clinics to make possible the further observation of those who would cooperate. Including normal individuals and patients with miscellaneous diseases used as controls, 575 blood cultures were taken on 459 persons. Of these arthritic patients, approximately two-thirds were first seen on the wards and one-third were ambulatory cases seen only in the clinics.

SUBDIVISION OF CASES

In a study having as its purpose the evaluation of various laboratory procedures as aids in differentiating various types of disease, an exact statement of the criteria by which cases were placed in the various groups is clearly essential. It should be emphasized, too, that only patients with obvious joint disease were included; those presenting neuritis, myositis, bursitis, and the like were excluded when the final analyses of the data were made. The following subdivisions were used, as convenient for the purposes of the investigation; they are not recommended as a perfectly satisfactory classification:

Rheumatic Fever with Polyarthrits.—The criteria for placing patients in this group were: (a) characteristic, migratory polyarthrits; (b) temperature of 103° F. or higher; (c) cardiac involvement as shown by precordial pain, prolonged atrioventricular conduction time, significant arrhythmias, or the development of characteristic valvular lesions; (d) characteristic response to amidopyrine; (e) recovery with no residual joint damage.

Atrophic (Rheumatoid) Arthritis.—This diagnosis was used in a narrower sense than that usually employed. All patients so listed showed: (a) progressive and recurrent polyarthrits of the type characterized by fusiform swelling of the joints, especially the metacarpophalangeal and proximal interphalangeal

joints of the hands, without overlying redness or periarticular induration; (b) only partial relief of joint pain following amidopyrine; (c) steadily progressive disease or partial recovery with residual deformity.

Gonococcal Arthritis.—These patients showed: (a) clinically characteristic arthritis occurring during the course of, or shortly following, a known gonococcal infection; or (b) similar arthritis without a history of recent gonococcal infection, but in patients with urethral or cervical smears showing typical gram-negative diplococci; no relief of pain following amidopyrine.

Hemolytic Streptococcal Arthritis.—Of the three patients in this group, two had typical brawny arthritis of the left shoulder during the course of known hemolytic streptococcal septicemia* and the third had clinically similar arthritis of the left knee containing frank pus from which hemolytic streptococci were repeatedly obtained in pure culture.

Nonspecific, Low-grade Pyogenic Arthritis.—These patients all had brawny induration of one or two joints which had the appearance of low-grade, pyogenic infections. In general they may be described as similar to the indurated type of gonococcal arthritis but were without any direct or indirect evidence of gonococcal infection. By many observers in this country these cases are included under the term atrophic (rheumatoid) arthritis but to us it seemed wise to list them separately on purely clinical grounds, at least for the purpose of these studies.

Hypertrophic (Osteo-) Arthritis.—(a) Cases of clinically characteristic arthritis of insidious onset in patients past middle age; (b) hypertrophic bony changes on roentgenographic examination; (c) erythrocyte sedimentation rates within normal limits or only very slightly above.

Miscellaneous Arthritis.—Included in this group were nine patients with spondylitis, four with gout, two with scurvy, and one each with tuberculous arthritis, Charcot's joint, Still's disease, traumatic arthritis, meningococcic arthritis, arthritis accompanying ulcerative colitis of unknown etiology, and arthritis accompanying amebiasis. The patients with spondylitis had involvement of no other joints; three were probably of osteoarthritic origin while the remaining six were of the type usually considered a subdivision of rheumatoid arthritis.

Unclassified Arthritis.—Almost one-fifth of the arthritic cases failed to fulfill the criteria as listed and, hence, were placed in an unclassified group. In some instances the nature of the joint disease was entirely unknown and such cases were listed as *wholly unclassified*. Most, however, were obviously of infectious origin although the type was not clear, and they were therefore listed as *unclassified infectious*. In many instances these cases could have been placed in one of the fixed categories with fair assurance, but since the diagnosis was not certain it was considered more accurate to segregate them. Included in the group of unclassified infectious cases were four patients with well-defined heart disease of the rheumatic type but with joint changes characteristic of rheumatoid arthritis.

*Hemolytic streptococci repeatedly grown in pure culture from the blood not only in broth but also in poured agar plates.

In addition to the subdivisions of patients with arthritis, five groups of controls were included as follows:

Normal Controls.—All normal individuals were members of the staff or medical students. Each was questioned concerning his recent health and those with illnesses during the preceding month were excluded.

Senescent Nonfebrile States.—A small group of patients with generalized arteriosclerosis, old hemiplegias and other degenerative diseases unaccompanied by fever was included. All were elderly and all were more or less cachetic.

Tonsillitis.—Only patients with typical acute tonsillitis with high fever, chills, tender regional lymph nodes, and red, swollen tonsils dotted with exudate were included. Throat cultures showed all to be caused by hemolytic streptococci. All blood cultures were taken within twenty-four hours of the temperature peak.

Other Hemolytic Streptococcus Diseases.—In this small group there were chiefly patients with puerperal or postabortal infections, erysipelas, and scarlet fever.

Active Rheumatic Carditis and Chorea.—Only patients with active disease but without polyarthritis were placed here.

TECHNIC OF BLOOD CULTURES

In order to make the work as objective as possible, the cultures were known only by number to the one (R.C.A.) who carried out all bacteriologic procedures subsequent to the venipuncture and inoculation of the primary cultures. Thus, the possibility that certain cultures might unconsciously be given more care than those of normal controls was excluded.

All initial cultures were taken soon after the patient came under observation and before the administration of antirheumatic drugs. Cultures were repeated, as a rule, only if relapses occurred. Thirty cubic centimeters or more of blood were withdrawn in carefully sterilized syringes. The area of skin to be punctured was painted with iodine which was allowed to dry and was then removed with alcohol; after the tourniquet was fastened a second application of iodine was allowed to dry and was not washed off until after the completion of the venipuncture. Covered with a sterile towel, the syringe was then carried directly to a bacteriologic laboratory where the media could be inoculated in suitable surroundings and with the aid of a Bunsen burner.

The first 152 cultures (Oct., 1932, to Jan., 1934) were done according to the aerobic method used by Callow.²⁹ Her technic was followed exactly even to the extent that all media were prepared by the same department which had made hers.* Five cubic centimeters of blood were inoculated into each of two bottles containing "double beef infusion broth." From one of these, subcultures were made after forty-eight hours and thereafter once weekly, into four tubes of media: "double beef infusion broth," dextrose (0.5 per cent) phosphate broth, "cooked meat beef heart broth," and phosphate (0.2 per cent) broth. After forty-eight hours these subcultures were examined in stained

*The authors are indebted to Dr. W. H. Park through whose kindness the media were obtained from the Department of Bacteriology, and to Miss Pauline Epstein and her associates who prepared them.

films and streaked on "double beef infusion" blood agar plates. The second bottle was not opened until the fourth week unless the first showed growth earlier. All original cultures were kept two months and were then centrifuged and the sediment examined in stained films and streaked on blood agar plates prior to being discarded. Further details of technic and the method of preparation of the media can be found in Callow's paper.²⁹

The next sixty cultures (Jan., 1934 to June, 1934) were done in duplicate by two methods: the first that just described and the second a modification of that recommended by Gray and Gowen,²¹ which is in turn a modification of the technic of Cecil, Nicholls and Stainsby.¹¹ By this method, 30 c.c. of blood were allowed to clot and the serum was removed. The clot was then broken up under sterile conditions and was transferred to a bottle containing 50 c.c. of broth prepared as described by Gray and Gowen. Subcultures were made after forty-eight hours and subsequently to the four media used for the cultures of whole blood.

Because the second method gave a somewhat higher percentage of positive results in these sixty patients and because it freed the serum from an additional 10 c.c. of blood for use in the serologic part of the study, the method using whole blood was discontinued and all remaining cultures were done by the clot method alone.

RESULTS

An analysis of the results obtained in the entire series is given in Table II, which is, for the most part, self-explanatory. In the table all results are shown

TABLE II

RESULTS OF BLOOD CULTURES IN PATIENTS WITH VARIOUS TYPES OF ARTHRITIS AND CONTROLS

	NUMBER OF CULTURES	NUMBER OF PATIENTS	PATIENTS POSITIVE	PATIENTS SHOWING			
				HEMOLYTIC STREP.	GREEN STREP.	INDIFFERENT STREP.	DIPH- THEROID BACILLI
			PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Normal controls	45	44	5		5		
Senescent nonfebrile states	9	8	25		25		
Tonsillitis (hemolytic streptococcal)	74	61	51	31	15	1	2
Other hemolytic streptococcal diseases	16	14	71	43	22		6
Active rheumatic carditis and chorea	27	22	18	4	14		
Rheumatic fever with polyarthritis	109	90	16	3	12	1	
Atrophic (rheumatoid) arthritis	48	35	19	3	9	5	3
Gonococcal arthritis	46	33	15	9*	6		
Hemolytic streptococcal arthritis	3	3	100	100			
Nonspecific, low-grade pyogenic arthritis	27	22	5		5		
Osteoarthritis	46	39	10		10		
Miscellaneous arthritis (gout, spondylitis, tuberculous, etc.)	29	22	15	5	10		
Unclassified arthritis							
Unclassified infectious arthritis	57	40	11	5	3		3
Wholly unclassified arthritis	39	28	14		6	4	4
Total	575	459					

Percentages are shown as the nearest whole numbers.

*One of these 3 patients had terminal mixed gonococcal and hemolytic streptococcal septicemia.

on a percentage basis; this was done for the sake of easy comparison of results in the different subdivisions even though some of the latter contained too few patients for percentages to be significant. The almost uniformly negative cultures of the normal individuals (2 positive of 44 persons) was in marked contrast to the high percentages of positive results in the patients with purulent hemolytic streptococcal arthritis, acute tonsillitis, and other known hemolytic streptococcal diseases. The next highest figure was obtained in the patients with nonfebrile, senescent diseases, but the group was too small for this unexpected result to be significant. With the exception of the twenty-two patients with nonspecific, low-grade, pyogenic arthritis, of whom only one gave a positive blood culture, the results in the remaining subdivisions were strikingly uniform, not only as to totals but also as to the nature of the microorganisms isolated.

Although all cultures were kept sixty days, the value of such long incubation was questionable. Of the 575 cultures, 138 were positive and of these 80 showed growth within forty-eight hours, 109 within one week, and 122 within two weeks. Of the remaining 16 cultures which were positive after longer incubation, only one gave a hemolytic streptococcus, the others being green and indifferent streptococci and diphtheroid bacilli. In four instances, only one of the two bottles was positive and in these, no growth was obtained until the bottles had been opened several times.

In eighty patients, more than one blood culture was taken, and of these twelve gave positive results. However, in only four instances was more than one culture positive for a given patient, and in one of these the microorganisms isolated at the two times differed in their effect upon red blood cells.

All streptococci were carefully studied before they were subdivided into hemolytic, green, and indifferent groups. This was particularly true in the case of those isolated from patients with rheumatoid arthritis because of the finding of Cecil, Nicholls and Stainsby¹¹ that their "typical strains" obtained from patients with that disease appeared to be green at first although they proved eventually to be hemolytic. When any question arose, strains were extracted chemically and were tested against known hemolytic streptococcal (Group A) antiserum by the method of Lancefield.³¹

Other than the microorganisms listed in Table II, staphylococci were found in twenty instances, gram-negative bacilli in six, and gram-positive bacilli in six. These occurred with approximately equal frequency in the various groups and were considered contaminants. Diphtheroid bacilli were listed in the table because of the frequency with which they have been considered significant in other studies. Among the patients with gonococcal arthritis, the gonococcus was obtained at blood culture in only one instance and this patient had frank gonococcal septicemia with mixed hemolytic streptococcal septicemia as a terminal event.

In Table II, as stated, the average results are shown for the entire series of cultures taken during the period October, 1932, to August, 1935. Toward the latter part of the study, however, it appeared that the percentage of positive cultures was decreasing. To test this impression a comparison was made

of results obtained with the clot method during the seven-month period from the time this method was begun in January, 1934, to August, 1934, and during the ten-month period from October, 1934, to August, 1935, the dividing line between the two periods being the summer months when work was temporarily discontinued. This comparison revealed the striking difference in results recorded in Table III.

DISCUSSION

The explanation of the divergent results illustrated in Table III is far from clear. The two series of cultures were small for statistical comparison; yet the differences noted were so consistent between the various subdivisions of the two series that pure chance seems an unlikely explanation. Each series covered approximately the same seasons of the year and the severity of the diseases in each was comparable. Furthermore, no changes had been made in technic and all the media had been prepared by the same department throughout. Other explanations naturally suggest themselves, such as the possibility that the higher figures of the first series were due to the introduction of streptococci as contaminants, or that the lower figures of the second series were caused by some technical error such as faulty media. Whatever the explanation, the lack of uniformity in results at different periods of this study is in keeping with the even greater differences between results obtained by various investigators as shown in Table I. In spite of the possible faults of the data presented, certain of the findings recorded in Table II are worthy of comment.

Certainly the results do not support the view that streptococci can be isolated from the blood in rheumatic fever and rheumatoid arthritis more frequently than in miscellaneous diseases. Neither do they bear out the theory that strains obtained from patients with these two diseases differ and that hemolytic streptococci predominate in rheumatoid arthritis. Hemolytic streptococci were only rarely isolated in this disease, yet the results in patients with known hemolytic streptococcal infections showed that the cultural methods were adequate for the isolation of these microorganisms. The results obtained in these subdivisions are of greater significance when it is recalled that cultures were known only by number throughout the bacteriologic procedures.

The success with which positive cultures were obtained in cases of tonsillitis was surprising in view of negative results of other workers. Callow²⁹ reported positive cultures in 66 per cent of eighteen patients with tonsillitis, but green streptococci and pleomorphic bacilli were the only microorganisms isolated. In the present series of sixty-one patients, on the other hand, hemolytic streptococci predominated and the frequency with which green streptococci were isolated was comparable to that noted in the other diseases studied. If borne out by future investigations, these results will confirm the generally accepted belief that bacteremia exists early in tonsillitis. Further work is in progress to check these results and to study the relationship between strains isolated from the throat and blood of individual patients.

The almost uniformly negative cultures in patients with joint disease of the type referred to as nonspecific, low-grade pyogenic arthritis, were surprising.

TABLE III
COMPARISON OF RESULTS OF BLOOD CULTURES DONE BY CLOT METHOD DURING TWO DIFFERENT PERIODS

	CULTURES TAKEN FROM JANUARY, 1934, TO AUGUST, 1934						CULTURES TAKEN FROM OCTOBER, 1934, TO AUGUST, 1935					
	NO. OF CULTURES	NO. OF PATIENTS	PATIENTS POSITIVE PER CENT	PATIENTS SHOWING			NO. OF CULTURES	NO. OF PATIENTS	PATIENTS POSITIVE PER CENT	PATIENTS SHOWING		
				HEMOL. STREPT. PER CENT	GREEN STREPT. PER CENT	INDIFF. STREPT. PER CENT				HEMOL. STREPT. PER CENT	GREEN STREPT. PER CENT	INDIFF. STREPT. PER CENT
Normal controls	10	10	20	0	20	0	27	26	0	0	0	0
Tonsillitis	9	9	55	22	33	0	10	10	20	0	0	0
Rheumatic fever with polyarthritis	15	13	30	7	23	0	51	38	5	0	5	0
Atrophic (rheumatoid) arthritis	23	19	25	5	10	10	19	13	7	0	7	0
Gonococcal arthritis	19	15	27	20*	7	0	23	19	0	0	0	0
Nonspecific, low-grade pyogenic arthritis	9	8	0	0	0	0	13	10	0	0	0	0
Hypertrophic (osteo-) arthritis	16	16	19	0	19	0	23	22	5	0	5	0
Totals	101	90					166	138				

*One patient had terminal mixed gonococcal and hemolytic streptococcal septicemia.

It had been the authors' expectation that these cases, sometimes called "focus type" or "metastatic" arthritis, would be associated with positive blood cultures more often than other types, since it is usually thought that the joint infection arises from bacteria carried by the blood from some distant focus of infection. Certainly the findings in this small group of 22 patients do not indicate that bacteremia exists in these cases, at least after the development of the joint infection.

Finally, the results obtained suggest that, if large quantities of blood and suitable methods are used, streptococci can occasionally be isolated from the blood of even normal persons; and that in individuals whose resistance has been lowered by illness, the percentage of positive cultures is increased. As noted by Lichtman and Gross,²⁷ Callow,²⁹ and others, these results do not suggest that the microorganisms isolated from patients with rheumatic fever and atrophic (rheumatoid) arthritis were the cause of the diseases in those patients, in view of the fact that similar results were obtained in diseases known to have other causes.

SUMMARY

As part of a bacteriologic and serologic study of arthritis, blood cultures were done on 310 patients with various types of joint disease and 149 controls. A clot method freed serum for use in serologic work but was not otherwise superior to one using whole blood. Prolonged incubation increased the percentage of positive cultures only slightly over that obtained by incubation for two weeks. Hemolytic streptococci were isolated frequently in tonsillitis and other known hemolytic streptococcal infections. Positive cultures were obtained in 10 to 19 per cent of patients with rheumatic fever, atrophic (rheumatoid) arthritis, gonococcal arthritis, and hypertrophic (osteo-) arthritis; the microorganisms obtained were chiefly green streptococci and less frequently hemolytic and indifferent streptococci and diphtheroid bacilli. The results did not suggest that the microorganisms isolated were the cause of arthritis in the patients from whom they were obtained. With the exception of the small group of patients with hemolytic streptococcal arthritis associated with frank septicemia, blood cultures were of no value in differentiating the various forms of arthritis studied.

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BACTERIOLOGIC AND IMMUNOLOGIC STUDIES IN ARTHRITIS*

II. RESULTS OF VARIOUS IMMUNOLOGIC TESTS IN DIFFERENT FORMS OF ARTHRITIS

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IN THE preceding paper¹ are given the results of blood cultures in different forms of arthritis done as part of a general study of methods which might aid in the differentiation of these diseases. As part of the same investigation, certain immunologic tests were included in the routine study of all arthritic patients, and it is the purpose of the present paper to report the results obtained. These procedures, all of which had been developed and previously applied to the study of arthritis by others, consisted of gonococcus complement fixation and hemolytic streptococcus agglutination and precipitation tests, and antistreptolysin and anti-fibrinolysin determinations.

The patients studied were those comprising the groups already described in the preceding paper.¹ However, since certain of the tests were added during the course of the investigation, not all were performed on every patient. The subdivisions of arthritis were the same as used previously, as were the criteria for placing patients in the various groups.¹ In this regard it should be emphasized that the tests under investigation were never used in classifying cases. The necessity of adhering strictly to this rule is obvious since the purpose of the study was to evaluate the tests as aids in differentiation. In the case of gonococcus complement fixation, however, a positive reaction in a patient whose diagnosis was uncertain sometimes led to clinical or bacteriologic findings which had previously been missed and which allowed the case to be correctly classified. As in the study of blood cultures, all doubtful cases were placed in the unclassified group.

The methods and results will be described separately for each test.

GONOCOCCUS COMPLEMENT FIXATION TESTS

Although the gonococcus complement fixation reaction has been known and used in the diagnosis of gonococcal infections for many years, conflicting reports of its value are still seen. The belief that positive reactions are significant but negative ones of no value has arisen from the experience of urologists that known gonococcal urethritis may exist in the face of negative complement fixation. As noted by Price,² however, it has been shown that, while a large percentage of patients with early, localized anterior urethritis show negative reactions, the more chronic and more systemic infections tend to give positive fixation. Since joint involvement indicates that the disease has become systemic, it would be expected

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that cases of gonococcal arthritis would show positive complement fixation, and this has been borne out by a number of studies.^{3, 4, 5}

Method.—The technic for performing the tests was that described by Park and Williams.⁶ Standardized reagents were kindly furnished by Dr. Annis Thompson of the Bureau of Laboratories of the City of New York. The gonococcus antigen was prepared according to the method of McNeal.⁷ Each test was controlled with known positive and negative serums.

Results.—The number of patients and the results obtained are recorded in Table I.

TABLE I

GONOCOCCUS COMPLEMENT FIXATION SHOWN BY SERUMS OF ARTHRITIC PATIENTS AND CONTROLS

	NUMBER OF SERUMS	NUMBER OF PA- TIENTS	PA- TIENTS POSI- TIVE	PATIENTS SHOWING FOLLOWING REACTIONS				
				±	+	++	+++	++++
			PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Normal controls	36	35	0					
Miscellaneous diseases	74	69	6		1	1		4*
Active rheumatic carditis and chorea	34	23	5				5	
Rheumatic fever with polyarthritis	113	70	7		6	1		
Atrophic (rheumatoid) arthritis	65	39	3	3				
Gonococcal arthritis	88	44	98	7	2	36	33	20
Nonspecific, low-grade pyogenic arthritis	41	30	0					
Osteoarthritis	58	48	2	2				
Miscellaneous arthritis (gout, spondylitis, tuberculous, etc.)	55	36	3*			3*		
Unclassified arthritis								
Unclassified infectious arthritis	71	44	12		5	7		
Wholly unclassified arthritis	42	30	0					
Totals	677	468						

Percentages are shown as nearest whole numbers.

*Meningococcus meningitis.

The percentage of patients with gonococcal arthritis in this series whose serums fixed complement (98 per cent) is higher than that reported by others. The reason for this is not clear but perhaps a partial explanation lies in the fact that tests were repeated at intervals, if negative at the first bleeding. In several instances, for example, positive reactions were not obtained until the third bleedings, without which these cases would have been recorded as negative.

It will be noted that a number of patients with positive gonococcus fixation reactions were listed in the unclassified groups. Probably several of these had gonococcal arthritis but as they did not fulfill the requirements set for such a diagnosis (see paper I, page 457), they were listed as shown. That such positive complement fixation does not necessarily give the diagnosis of the joint disease is obvious, as illustrated by the patients with unquestionable rheumatic fever who happened to have coincidental gonococcal infections. The tests were, however, of great value, and it is felt, not only that positive results are important in establishing the diagnosis of gonococcal arthritis in a patient with joint disease, but also that repeatedly negative reactions are highly significant in excluding it.

HEMOLYTIC STREPTOCOCCUS AGGLUTINATION TESTS

Interest in hemolytic streptococci as the possible cause of rheumatoid arthritis received great impetus from the success of Cecil, Nicholls, and Stainsby⁸ in isolating these microorganisms from blood cultures of patients with that disease. Subsequently the same authors^{9, 10} showed that serums of atrophic (rheumatoid) arthritic patients agglutinated their "typical strains" of hemolytic streptococci in high titers. In the same year, however, Dawson, Olmstead and Boots¹¹ demonstrated that such agglutinability is not limited to the "typical strains" of Cecil, Nicholls and Stainsby, but is common to hemolytic streptococci isolated from patients with a variety of diseases. Thus, although the results no longer supported the theory that a specific kind of hemolytic streptococcus was the cause of atrophic (rheumatoid) arthritis, the test was confirmed as of diagnostic importance in distinguishing this disease from other forms of arthritis. This has been confirmed in general, by the studies of Gray and Gowen,¹² Ashworth,¹³ Keefer, Myers and Oppel,¹⁴ Cox and Hill,¹⁵ Wainwright,¹⁶ and Blair and Hallman.¹⁷ The results of Clawson and his coworkers¹⁸ do not bear on the question since the strains used by them for agglutination apparently were not hemolytic.

Method.—The method followed and the criteria used in reading the tests were those described by Dawson, Olmstead and Boots¹¹ whose article may be consulted by those wishing the details of technic. Following is a summary of the method: Twenty-hour broth cultures of hemolytic streptococci in quantities of 0.5 c.c. were mixed with equal amounts of the various serum dilutions. Tests were read after incubation two hours in the water-bath at 56° C. and refrigeration overnight. The final dilutions were 1 to 20 through 1 to 640; since these six proved sufficient, higher dilutions were only rarely used. In the early part of the work, strain AB 13, kindly provided by Dr. Stainsby, was used, but was abandoned because, in our hands, it not infrequently agglutinated spontaneously in control tests with normal serums. After trial of a number of strains, all of which were more or less satisfactory, the well-known hemolytic streptococcus, NY 5, originally isolated from the throat of a patient with scarlet fever, was selected for routine use. Occasionally, stock broth cultures kept in the ice box for long periods tended to give rise to granular suspensions, in which case it was found important to discard them and start afresh with new cultures from the frozen and dried stocks.¹⁹

Results.—With this technic, results of great uniformity were obtained, as shown in Table II. The finding of others that hemolytic streptococci are agglutinated by serums of patients with atrophic (rheumatoid) arthritis is strikingly confirmed; indeed, the percentage of such patients showing agglutination in this series is higher than that in most other reports. This is perhaps due to the fact that in many clinics the name atrophic (rheumatoid) arthritis is given to cases of joint disease of the type here referred to as nonspecific, low-grade pyogenic arthritis; and these patients in the present study gave uniformly negative agglutination. Whether this supports the clinical impression of the authors that these two groups of cases should be distinguished cannot, of course, be stated until the significance of hemolytic streptococcus agglutination in atrophic

(rheumatoid) arthritis is understood. Serums of six patients with spondylitis of the ankylopoetica type without other joint involvement likewise gave negative results.

It is apparent from an examination of reports on the use of this procedure in the diagnosis of arthritis that the decision as to what constitutes a significant titer depends on the strain of hemolytic streptococcus used. Cox and Hill,¹⁵

TABLE II

AGGLUTINATION OF HEMOLYTIC STREPTOCOCCUS BY SERUMS OF ARTHRITIC PATIENTS AND CONTROLS

#	NUMBER OF SERUMS	NUMBER OF PA- TIENTS	PA- TIENTS POSI- TIVE	PATIENTS POSITIVE AT DILUTION					
				1-20	1-40	1-80	1-160	1-320	1-640
			PER CENT*	PER CENT*	PER CENT*	PER CENT*	PER CENT*	PER CENT*	PER CENT*
Normal controls	36	35	0						
Hemolytic streptococcal dis- eases	20	11	27	9	9				9
Active rheumatic carditis and chorea	40	25	0						
Rheumatic fever with poly- arthritis	112	71	5	1	1	3			
Atrophic (rheumatoid) ar- thritis, disease active	79	36	86	6	3	20	8	6	42
Atrophic (rheumatoid) ar- thritis, disease inactive	3	3	0						
Gonococcal arthritis	81	42	4		2†			2†	
Hemolytic streptococcal ar- thritis	2	2	50		50				
Nonspecific, low-grade pyo- genic arthritis	40	29	0						
Osteoarthritis	59	46	0						
Miscellaneous arthritis (gout, spondylitis, tu- berculous, etc.)	50	29	0						
Unclassified arthritis									
Unclassified infectious ar- thritis	72	44	14	2		5		2	5
Wholly unclassified arthri- tis	41	30	0						
Total	635	403							

Percentages are shown as nearest whole numbers.

*Figures designate percentages of patients whose serums caused agglutination to the titers shown at the heads of the respective columns.

†Negative at seven subsequent bleedings.

‡This patient also had hemolytic streptococcal septicemia.

using a "typical strain" of Ceecil, Nicholls and Stainsby frequently observed agglutination in the lower dilutions of serums from patients with other forms of arthritis, while the results of this series confirm the finding of Dawson, Olmstead and Boots¹¹ that with strain NY 5 agglutination is limited almost entirely to those with the rheumatoid type. It is clear, furthermore, that even using the same strains, different workers will obtain somewhat varied results because of differences in media and other factors. This lack of absolute agreement, however, in no way affects the general conclusion that the test is peculiarly selective for atrophic (rheumatoid) arthritis.

That hemolytic streptococci are agglutinated by serums of occasional patients with typical rheumatic fever and known hemolytic streptococcal infections, as shown in the table, is not surprising. Our results using strain NY 5, however, did not agree with Coburn and Pauli's²⁰ observation that serums of most patients acutely ill with rheumatic fever or known hemolytic streptococcal infections agglutinated hemolytic streptococci to a titer of 1:10 to 1:40. Indeed, the great frequency and relatively high titers of agglutination in atrophic (rheumatoid) arthritis contrasted with its rarity in known hemolytic streptococcal diseases raises a doubt as to the etiologic significance of the test in the former.

HEMOLYTIC STREPTOCOCCUS PRECIPITATION TESTS

Antigenically, hemolytic streptococci have been shown by Lancefield²¹⁻²⁴ to be complex mosaics containing, among other fractions, a "nucleoprotein" (P) which is not specific as it gives cross precipitation with other gram-positive cocci, a group-specific carbohydrate (C), and type-specific protein and carbohydrate fractions (M and S). Seegal, Heidelberger, Jost and Lyttle²⁵ in 1933 showed that nucleoprotein fractions and the C-substance of hemolytic streptococci from human infections, precipitate serums of patients with atrophic (rheumatoid) arthritis; and this was confirmed in greater detail by Dawson, Olmstead and Jost.²⁶ Coburn and Pauli²⁰ had previously obtained similar results in active rheumatic fever using the nucleoprotein fractions, but only rarely with C. Schlesinger and Signy²⁷ also reported positive precipitation reactions with the serums of actively rheumatic children, using a simple saline extract of pulverized hemolytic streptococci. Because of the greater specificity of the C-substance, it was selected for the precipitation tests of the present study. The nucleoprotein has been used as well, but in too few cases to warrant reporting the results at this time.

Method.—Crude C extract was prepared from strain NY 5 by Lancefield's method.²³ Four-tenths, 0.1, 0.025, and 0.01 c.c. of this were made up to volumes of 0.4 c.c. with physiologic saline, and to each tube was added 0.2 c.c. of the serum to be tested. Control tubes of extract and serums alone were included in each test. All tubes were incubated in the water-bath at 37° C. for two hours and then refrigerated overnight. At first the readings next morning were made before and after centrifugation, but the former were so seldom positive that this reading was later omitted.

Results.—The results are summarized in Table III. Because preliminary studies in known hemolytic streptococcal diseases showed that precipitins frequently did not appear until the fourth week of illness, no patient with negative reactions was included in the analysis of results unless at least one bleeding was obtained after the thirtieth day of disease. The same requirement was set in the antistreptolysin and antifibrinolysin tests which are described later.

Although precipitation was most frequently and strongly positive in the case of known hemolytic streptococcal diseases, atrophic (rheumatoid) arthritis and rheumatic fever, many patients of the other groups showed positive reactions as did 5 (24 per cent) of the 21 supposedly normal individuals. Thus the test was of little value in differentiating between the various groups of arthritis in this

study. It should be mentioned, too, that serums of four patients with bacterial endocarditis due to green streptococci (not included in the table) gave strongly positive precipitation with the crude C extract of hemolytic streptococci, as was noted previously by Seegal, Heidelberger, Jost and Lyttle.²⁵

TABLE III
PRECIPITIN REACTIONS BETWEEN CRUDE "C" EXTRACT OF HEMOLYTIC STREPTOCOCCUS (GROUP A) AND SERUMS OF ARTHRITIC PATIENTS AND CONTROLS

	NUMBER OF SERUMS	NUMBER OF PA- TIENTS	PA- TIENTS POSI- TIVE	PATIENTS SHOWING FOLLOWING REACTIONS			
				+	++	+++	++++
			PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Normal controls	22	21	24	14	5	5	
Hemolytic streptococcal diseases	14	8	62	12	12	12	25
Active rheumatic carditis and chorea	14	9	55	33	11		11
Rheumatic fever with polyarthritis	69	39	56	23	2	8	23
Atrophic (rheumatoid) arthritis, disease active	36	22	77	36	18		23
Gonococcal arthritis	32	19	32	32			
Nonspecific, low-grade pyogenic arthritis	17	13	31		23		8
Osteoarthritis	35	30	18	7	7	4	
Miscellaneous arthritis (gout, spondylitis, tuberculous, etc.)	19	16	12	12			
Unclassified arthritis							
Unclassified infectious arthritis	36	26	46	23	9	9	5
Wholly unclassified arthritis	26	20	58	33	8	8	8
Total	338	223					

Percentages are shown as nearest whole numbers.

ANTISTREPTOLYSIN DETERMINATIONS

Todd²⁸ in 1931 showed that streptococcal hemolysin is antigenic when suitably prepared, and that it gives rise to a species-specific antibody. Later he²⁹ showed the presence of this antibody (antistreptolysin) to be present only following hemolytic streptococcal infection; and both he²⁹ and Coburn and Pauli²⁰ reported high antistreptolysin titers to be constant findings in patients with active rheumatic fever. Myers and Keefer³⁰ found the antistreptolysin titer generally high but not constantly so in known hemolytic streptococcal diseases and rheumatic fever, but within normal limits in a few patients with atrophic (rheumatoid), gonococcal and hypertrophic (osteo-) arthritis. Wilson, Wheeler and Leask,³¹ reporting their experience with antistreptolysin determinations in rheumatic children, concluded that a rise in titer is not a necessary accompaniment in such patients. Recently Blair and Hallman¹⁷ obtained results similar to those of Myers and Keefer except that antistreptolysin titers definitely above normal were found in about one-third of their cases of atrophic (rheumatoid) arthritis.

Method.—The technic used was that of Hodge and Swift,* to whose article³² the reader is referred for details. With this method, remarkably constant results were obtained with different lots of streptolysin throughout the study. Only pa-

*Serum and streptolysin of known titers were kindly provided by Dr. Homer F. Swift and Dr. B. E. Hodge for the determination of standards for this study.

TABLE IV
ANTISTREPTOLYSIN TITERS SHOWN BY SERUMS OF ARTHRITIC PATIENTS AND CONTROLS

	NUMBER OF SERUMS	NUMBER OF PATIENTS	PATIENTS SHOWING UNITS ANTISTREPTOLYSIN													
			<25	25	50	100	150	200	250	300	350	400	450	500	>500	
Normal controls	38	37	% 11	% 40	% 43	% 3	% 3									
Hemolytic streptococcal diseases	57	30		7	10	23	17	7	7	8	16	8	3	13	3	
Active rheumatic carditis and chorea	22	14		8	16	16	8	16	8	16	8	16	8	8	10	
Rheumatic fever with polyarthritides	88	51		2	2	16	14	14	14	18	8	8	8	8	4	
Atrophic (rheumatoid) arthritis	51	36	6	47	18	18	6	6	3							
Gonococcal arthritis	63	38	5	29	40	9	9	3								
Nonspecific, low-grade pyogenic arthritis	30	21	15	29	46	10										
Osteoarthritis	57	46	18	41	34	7										
Miscellaneous arthritis (gout, spondylitis, tuberculous, etc.)	30	25	17	28	28	22										
Unclassified arthritis																
Unclassified infectious arthritis	59	40	5	13	25	25	13	7	2	7						
Wholly unclassified arthritis	43	31	4	13	48	22	9		4					2		
Total	538	369													5*	

Percentages are shown as nearest whole numbers.

*Arthritis occurring during course of meningococcal meningitis.

†Blood culture positive for hemolytic streptococcus in one of these two patients.

tients who had test bleedings over a period of at least one month after the onset of illness were included in the analysis, the average in the arthritic groups being two and one-half months.

Results.—As shown in Table IV, all but two of the normal individuals gave readings of 50 units of antistreptolysin or less; however, it seemed best for the present to consider only titers above 150 units abnormal. Examination of the table shows that the readings above this figure were limited almost entirely to the patients with known hemolytic streptococcal diseases and active rheumatic fever without and with polyarthritis. The percentages of patients in these three groups with titers in the abnormal range were 43 per cent, 56 per cent, and 65 per cent, respectively. The percentage in the group of known hemolytic streptococcal cases (most of which were scarlet fever*) was lower than had been expected. Probably it would have been higher had the patients been followed longer than the one-month period usual for this control group.

Only two patients with atrophic (rheumatoid) arthritis gave high titers. Of the two cases of gonococcal arthritis with antistreptolysin titers of 450 units, one was easily explained since the patient had a mixed gonococcal and hemolytic streptococcal septicemia; no explanation was apparent, however, for the high reading in the second case. Likewise, no reason could be found for the titer of over 500 units in a patient whose arthritis appeared during the course of meningococcal bacteremia. An interesting question naturally arises as to whether the eight patients with unclassified arthritis who showed readings in the abnormal range actually had atypical rheumatic fever.

It is clear that antistreptolysin titers were high in the majority of patients with rheumatic fever in this series, and it is probable that the percentage would have been even higher had the patients been followed still longer. On the other hand, the titer did not rise above 25 units in one unquestionable case followed more than two months.

ANTIFIBRINOLYSIN DETERMINATIONS

In 1933 Tillett and Garner³³ reported studies on the ability of hemolytic streptococci to liquefy normal human fibrin clot, and the following year³⁴ described the capacity of plasma clots from the blood of patients convalescent from acute hemolytic streptococcal infections to resist this fibrinolytic action. Hadfield, Magee and Perry³⁵ used the procedure in studying rheumatic children and found that in 48 per cent of 21 patients with active disease the clots were resistant to fibrinolysis whereas in all of 23 quiescent and 26 normal children the clots were susceptible. Myers, Keefer and Holmes³⁶ applied the test in a number of diseases and found the clots of practically all patients with known hemolytic streptococcal diseases and rheumatic fever more or less resistant while those of normal individuals were less resistant or susceptible. Their results in atrophic (rheumatoid) and gonococcal arthritis were similar to the normal except that occasional clots showed high resistance.

*The serums from patients with scarlet fever were obtained from the Williard Parker Hospital, New York City.

Method.—The technic of Tillett, Edwards and Garner^{34*} was followed exactly. Their classification of the degree of susceptibility of the clot was employed:

Dissolution in less than 30 minutes	Highly susceptible
Dissolution in 30 to 60 minutes	Susceptible
Dissolution in 1 to 8 hours	Definite resistance
Dissolution in 8 to 24 hours	Marked resistance
No dissolution in 24 hours	Maximum resistance

Only patients whose test bleedings covered a period of at least one month after the onset of disease were included.

TABLE V
ANTIFIBRINOLYTIC ACTIVITY OF SERUMS OF ARTHRITIC PATIENTS AND CONTROLS

	NUMBER OF SERUMS	NUMBER OF PA- TIENTS	PER CENT PATIENTS WHOSE CLOTS DIS- SOLVED IN TIME SHOWN				
			< 1/2 HR.	1/2-1 HR.	1-8 HR.	8-24 HR.	> 24 HR.
Normal controls	17	17	PER CENT 24	PER CENT 12	PER CENT 59	PER CENT	PER CENT 6
Hemolytic streptococcal disease	10	3					100
Active rheumatic carditis and chorea	10	6			66		33
Rheumatic fever with polyarthri- tis	43	29	10	3	14	14	59
Atrophic (rheumatoid) arthritis	11	11	18	27	36		18
Gonococcal arthritis	10	10	50	10	10		20
Nonspecific, low-grade pyogenic arthritis	11	8	50		38		12
Osteoarthritis	13	13	54	8	38		
Miscellaneous arthritis (gout, spondylitis, tuberculous, etc.)	13	11	36		27	9	27
Unclassified arthritis							
Unclassified infectious arthritis	25	19	27		27		46
Wholly unclassified arthritis	15	15	47		40	7	7
Total	178	146					

Percentages are shown as the nearest whole numbers.

Results.—The results, summarized in Table V, were very similar to those obtained by Myers, Keefer and Holmes.³⁶ In general, they tended to parallel those of antistreptolysin determinations but were less clear-cut in separating the various groups. The percentage of normal individuals in this small series whose clots did not liquefy within one hour was more than twice that reported by Tillett, Edwards and Garner.³⁴ This is perhaps due to a greater incidence of unnoticed mild hemolytic streptococcal infections in New York than in Baltimore, where their observations were made.

DISCUSSION

In view of the etiologic significance of the gonococcus complement fixation reaction in the type of arthritis in which it is generally positive, a question naturally arises as to the possibility of a similar significance for the other tests here described in rheumatic fever and atrophic (rheumatoid) arthritis. The

*Through the kindness of Dr. William S. Tillett a culture of hemolytic streptococcus, CO., was obtained for use in these tests.

results of agglutination tend to implicate the hemolytic streptococcus in atrophic (rheumatoid) arthritis but are usually negative in rheumatic fever; the reverse, however, is true for the antistreptolysin and antifibrinolysin tests, while precipitation reactions with hemolytic streptococcal fractions tend to be positive in both diseases. Other than to point out that these apparently contradictory results are actually not immunologically inconsistent, this phase of the problem will not be discussed further here. Neither can the bearing of the tests on the problem of relationship between rheumatic fever and atrophic (rheumatoid) arthritis be discussed in this paper which is concerned chiefly with the possible value of these procedures as differential diagnostic aids.

In the case of gonococcus complement fixation, hemolytic streptococcus agglutination and antistreptolysin tests, the results in this series of cases were sufficiently selective of certain forms of arthritis to warrant their further use as diagnostic aids. Hemolytic streptococcus precipitin and antifibrinolysin reactions tended to give results paralleling those of agglutination and antistreptolysin determinations respectively, but were far less selective. In Table VI are shown

TABLE VI

SCHEMATIC REPRESENTATION OF TENDENCIES SHOWN BY GONOCOCCUS COMPLEMENT FIXATION, HEMOLYTIC STREPTOCOCCUS AGGLUTINATION AND ANTISTREPTOLYSIN TESTS IN VARIOUS TYPES OF ARTHRITIS

	GONOCOCCUS COMPLEMENT FIXATION	HEMOLYTIC STREPTOCOCCUS AGGLUTINATION	ANTI- STREPTOLYSIN
Rheumatic fever with or without polyarthritis	—	—	+
Atrophic (rheumatoid) arthritis	—	+	—
Gonococcal arthritis	+	—	—
Nonspecific, low-grade pyogenic arthritis	—	—	—
Osteoarthritis	—	—	—
Gout, tuberculous arthritis, scurvy, etc.	—	—	—

the patterns of results obtained with the three more uniform tests in the various groups of joint diseases included in this study. With the addition of the erythrocyte sedimentation test to distinguish between osteoarthritis and what is here referred to as nonspecific, low-grade pyogenic arthritis, a literal acceptance of the tendencies represented in Table VI might lead to the conclusion that the time is at hand when a differential diagnosis in joint disease may be made without looking at the patient merely by sending a specimen of blood to the laboratory. Obviously such is far from the case, for the exceptions to the results in almost every category are sufficient to raise some doubt as to the specificity of the tests in question. Furthermore, the cases of classified arthritis on which the results reported here were based were all characteristic examples of their respective types and easily classified by purely clinical means. Hence, it follows that the results with the various tests might be fairly definite in these cases in which they are not necessary for diagnosis, and yet be vague in the less clearly defined and early cases in which help is most needed.

It must be emphasized, too, that the total experience with most of these technics is small thus far, and that objections may become apparent with their further use. Already, discrepancies have appeared in the results of various work-

ers. Cox and Hill,¹⁵ for example, obtained positive hemolytic streptococcus agglutination in a number of patients with osteoarthritis; Wilson, Wheeler and Leask³¹ apparently consider antistreptolysin determinations of little significance in rheumatic fever; and recently Blair and Hallman¹⁷ reported abnormally high antistreptolysin titers in almost one-third of their cases of atrophic (rheumatoid) arthritis. The lack of exact criteria for placing patients in the various arthritic groups adds to the difficulty of interpreting the results reported.

In spite of the obvious deficiencies of the tests at the present stage of their development, the authors believe that gonococcus complement fixation, hemolytic streptococcus agglutination and antistreptolysin determinations are distinctly useful in the study and differentiation of joint disease and that they might well be included as routine procedures in arthritis clinics.

This investigation is being continued with particular reference to clinically atypical, unclassified cases. It is hoped that by carefully following such patients over a period of years, the correct diagnoses may become clear in enough instances to warrant a decision as to the significance of positive tests in cases not diagnosable clinically. It may thus be learned whether these methods are of more than confirmatory value and may suggest a correct diagnosis earlier than would be possible without them.

SUMMARY

As part of a wider study of methods which might prove useful in the differential diagnosis of joint diseases, gonococcus complement fixation, hemolytic streptococcus agglutination and precipitation tests, and antistreptolysin and antifibrinolysin determinations were made on a series of patients with various types of arthritis. The results obtained with each have been discussed. The precipitation and antifibrinolysin tests in this study gave less selective results than the others. Gonococcus complement fixation reactions were positive in 98 per cent of 44 patients with gonococcal arthritis. The serums of 86 per cent of 36 patients with active atrophic (rheumatoid) arthritis agglutinated a hemolytic streptococcus. Antistreptolysin titers above normal were obtained in at least 66 per cent of 51 patients with rheumatic polyarthritis. These three tests were considered distinctly useful.

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DISCUSSION

DR. RUSSELL L. CECIL, NEW YORK, N. Y.—I am much interested in Dr. McEwen's report, particularly that part which has a bearing on studies which Nicholls, Stainsby and I published some years ago. Dr. McEwen's figures differ from ours in several respects. The percentage of positive blood cultures in the arthritic patients was lower and the percentage of positive cultures in the controls was higher than in our series.

Most of Dr. McEwen's strains were classified as viridans. In our study, we were at first dubious about the classification of these peculiar streptococci. In our preliminary report we called them viridans. After they had been kept under cultivation for some time, a good many of them took on hemolytic qualities. We should not allow ourselves to be confused by the terminologies of different workers, for many streptococci undergo mutations under certain conditions. The higher percentage of positive blood cultures in Dr. McEwen's control groups throws some light on this problem. In our original study I believe we made the mistake of not having a wider variety of controls. Most of them were either normal, healthy controls or patients with hypertrophic arthritis. In our normal healthy controls we had no positive cultures; in our other group we had a small percentage of positives. If we had run more controls on patients with other forms of infection, especially acute respiratory infections, we might have avoided that error.

I was particularly interested in Dr. McEwen's high percentage of positive agglutinations. I think the percentage of positive agglutinations to hemolytic streptococci with arthritic serum will depend on how the cases are selected. You will find both high positive cultures and high agglutinations if you are careful in selection of cases. If you are not careful the percentage will be low. It is interesting that in spite of the large group of controls that showed streptococci in the blood, the group of cases of atrophic arthritis is the only one that showed a high percentage of agglutination reactions. The significance of streptococci in the blood of arthritic patients is, of course, influenced somewhat by the presence of streptococci in controls. The next important problem in this field is to determine the origin of these streptococci. Dr. McEwen did not show, but I think he has evidence, as we had, that the streptococci are actually in the blood stream and not contaminations from the skin or air. We must find out how they get there.

DR. M. H. DAWSON, NEW YORK, N. Y.—May I say a few words regarding the reliability of the agglutination reaction with hemolytic streptococci in atrophic (rheumatoid) arthritis. Prior to July of last year we had tested the serums from 503 cases of atrophic (rheumatoid) arthritis and from 571 control cases and during the past year we have tested

several hundred more cases. In our experience the reaction is a most significant one and only occurs in atrophic (rheumatoid) arthritis or in severe hemolytic streptococcal infections. We have never found a positive reaction in any case of hypertrophic arthritis. We have found the test to be as valuable as the gonococcal complement fixation test in gonorrheal arthritis.

One would not expect to find the antistreptolysin and antifibrinolysin tests positive in a chronic disease such as atrophic (rheumatoid) arthritis. These tests are indices of recent acute hemolytic streptococcal infection. However, if one confines oneself to cases of early acute atrophic (rheumatoid) arthritis, one is impressed with the percentage of cases showing an increase in the antistreptolysin content of the serum.

DR. J. A. KEY, ST. LOUIS, MO.—I am surprised that no staphylococci grew in these cultures, even as contaminations. In doing synovectomies, I am still able to excise a piece of the synovial membrane, immediately put it in broth, and grow staphylococci therefrom in about one case in three. I have never gotten streptococci from a chronic arthritic joint. I do not know why they will not grow for me, but they do not.

I wonder whether or not cases that give a positive complement fixation test are really of gonorrheal arthritis. Would other gonorrheal infections present in the same individual account for positive tests? I wonder if a coincident (nongonorrheal) arthritis would not be called gonorrheal arthritis because a case gave a positive fixation test.

DR. JOHN W. GRAY, NEWARK, N. J.—Dr. McEwen's bacteriologic and serologic findings in atrophic (rheumatoid) arthritis are similar to ours. We have felt that our high percentage of blood cultures positive for streptococci was of significance and that positive agglutinations strengthened this assumption. In a small percentage of our cases the blood cultures showed staphylococci, and although further studies may show their relationship to the disease, we should, until that time, consider them contaminants.

DR. MCEWEN (closing).—We had a fair percentage of contaminants, and we occasionally noted staphylococci in cultures. We considered them contaminants and did not therefore include them in the table.

I agree with Dr. Dawson that antistreptolysin titers are apt to be high in patients with early atrophic (rheumatoid) arthritis, while they are seldom high in more advanced cases.

The possibility that positive gonococcus complement fixation tests might lead to a false diagnosis in some patients, was borne in mind. We therefore set strict criteria for the diagnosis of gonococcal arthritis. As I said in the beginning, the tests we were evaluating were not used in placing patients in the various groups. The gonococcus complement fixation test was an exception to this only in the sense that a positive result in a patient in whom gonococcal arthritis had not been suspected led us to examine him for further clinical evidence to establish that diagnosis.

Concerning Dr. Dawson's statement on the specificity of hemolytic streptococcus agglutination in atrophic (rheumatoid) arthritis, I would point out that occasional patients with rheumatic fever gave a positive agglutination reaction. This was only rarely encountered.

PROTEIN STUDIES IN ATROPHIC (RHEUMATOID) AND HYPERTROPHIC ARTHRITIS

JOHN STAIGE DAVIS, JR., M.D., NEW YORK, N. Y.

SINCE the reawakening of interest in the sedimentation rate by Robin Fareus¹ in 1918, there has been an immense amount of clinical and laboratory investigation concerning the chemical changes in the blood which are responsible for this phenomenon.

Boots, Dawson and Sia² have called attention to a difference in sedimentation rate in atrophic arthritis as opposed to that in hypertrophic arthritis. They stated that this was further evidence to show that these were two different and distinct diseases.

Snapper and others³ showed that the power of the red cells to settle at various rates in different diseases was dependent on three factors: i.e., cell volumes, plasma fibrinogen, and plasma globulin. If these three constituents be known, the sedimentation rate can be calculated with a fair degree of accuracy.

It was in an effort to determine just how these changes occur in the various types of arthritis that this work was undertaken. Also, it was hoped that by a study of the different globulin fractions of the plasma, some tangible means of determining the effect of various forms of treatment might be obtained. Rubinstein and Fischer,⁴ Hurwitz and Meyer,⁵ and others⁶ have shown that a rise in globulin, especially in the euglobulin fraction, could be obtained by the administration of typhoid vaccine and that such a rise occurs in bacterial infections. It was thought that a similar rise might be obtained from the administration of either hemolytic streptococcus vaccine or different types of autogenous vaccines in the treatment of arthritis. If such a rise would result then one would expect an increase in the sedimentation rate as desensitization took place, rather than a decrease, as is most commonly seen. The effects of several forms of treatment on the blood protein are now being studied and will be reported at a later date.

This paper will deal only with those changes which occur at various stages of the disease, arthritis.

MATERIAL AND METHODS

The total plasma protein, albumin, globulin, fibrinogen, globulin fractions pseudo I and II, and euglobulin and sedimentation rate have been determined on numerous occasions on ninety subjects. The cases are divided as follows:

Normals	9
Serious atrophic (rheumatoid) arthritis	15
Acute rheumatic fever	1
Arrested cases of atrophic (rheumatoid) arthritis	6
Mild cases of atrophic (rheumatoid) arthritis	20
Cases ill with other diseases than arthritis	6
Myositis	5
Cases of hypertrophic arthritis	14
	76

The protein contents have been determined on 220 samples of blood. This paper is based on the findings obtained from 76 of the 90 subjects concerning whom the diagnosis was definite. For example, those who were unfortunate enough to have both types of arthritis or those with gonorrheal arthritis are not included in this report.

The chemical analyses were done by Dr. Chandler in the Department of Physiology of the Cornell Medical School. The method of Howe has been used. The sedimentation rates were done according to modification of Westergren method; no correction for cell volumes has been made. The cases have been obtained from St. Luke's Hospital, the New York Post-Graduate Hospital, and from private practice.

RESULTS

In Table I are given the results obtained from an analysis of the blood of nine normals. These figures compare favorably with the average normal con-

TABLE I
NORMAL

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
W. B. E.	9/25/34	6.36	4.32	2.04	2.12	0.38	1.03	0.40	0.23	10
F. L.	6/27/34	6.38	4.46	1.92	2.32	0.34	1.31		0.27	
M. L.	6/27/34	7.35	5.22	2.13	2.35	0.33	1.13	0.13	0.54	
G. P.	10/30/34	6.87	4.43	2.44	1.81	0.43		0.54		10
P. H.	4/16/35	6.84	4.67	2.17	2.15	0.31	1.11	0.35	0.40	13
J. S. D.	3/12/34	6.40	4.18	2.22	1.88	0.30	1.32	0.40	0.20	
B. M.	11/20/34	7.33	4.93	2.40	2.05	0.50	1.26	0.41	0.23	15
C. C.	6/23/34	7.35	5.08	2.27	2.28	0.26	1.59		0.42	
E. S.	4/30/35	7.32	4.99	2.33	2.14	0.30	1.15	0.52	0.36	
Average		6.91	4.70	2.21	2.12	0.35	1.17	0.39	0.33	12

TABLE II
SEVERE ATROPHIC (RHEUMATOID) ARTHRITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
M. M.	2/20/34	7.54	3.56	3.98	0.90	0.68	1.89	0.66	0.75	
L. M.	2/27/34	7.22	3.59	3.63	0.99	0.84	1.58	0.71	0.50	125
T. F.	6/26/34	8.15	3.66	4.49	0.82	0.77	2.04	0.68	1.00	45
B. K.	5/ 8/35	5.70	2.32	3.38	0.69	0.58	1.70	0.53	0.57	
O. F.	3/ 2/34	7.75	3.89	3.86	1.01	0.57	2.49		0.80	97
C. K.	3/19/34	7.35	3.21	4.14	0.77	0.65	2.06	0.65	0.78	
E. L.	10/23/34	7.98	3.92	4.06	0.97	0.81	2.55		0.70	
O. O.	3/23/34	6.09	2.52	3.57	0.71	0.56	1.65	0.65	0.71	
L. H.	2/20/34	8.35	4.08	4.27	0.96	0.45	2.39	0.58	0.85	43
L.	3/12/34	6.73	3.01	3.72	0.81	0.61	1.61	0.80	0.70	120
H. L.	1/22/35	7.84	3.97	3.87	1.02	0.60	1.85	0.69	0.73	86
A. M.	4/27/34	6.64	3.44	3.20	1.07	0.62	1.33	0.55	0.70	
J. J.	6/12/34	7.74	3.45	4.29	0.80	0.89	1.53	0.90	0.97	
M. G.	2/20/34	7.35	3.74	3.61	1.04	0.39	1.86	0.68	0.68	104
M. C.	9/11/34	8.12	3.86	4.26	0.91	0.49	2.02	0.76	0.99	65 Rh. fever
E. F.	10/23/34	7.32	3.63	3.69	0.98	0.59	2.69		0.42	
Average		7.36	3.49	3.88	0.90	0.63	1.81	0.68	0.74	85

TABLE III
HYPERTROPHIC ARTHRITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
E. O.	5/ 1/34	6.75	4.25	2.51	1.69	0.20	1.39	0.57	0.44	5
E. S.	3/ 2/34	6.29	4.05	2.24	1.80	0.23	1.00	0.58	0.43	
J. H.	7/ 3/34	7.03	4.42	2.61	1.69		1.39	0.41	0.61	
D. K.	12/11/34	8.02	5.04	2.91	1.73	0.27	1.76	0.45	0.43	35
M. R.	4/17/34	6.90	4.34	2.56	1.70	0.32	1.28	0.54	0.42	45
M. Z.	3/13/34	6.57	4.06	2.51	1.62	0.13		2.27	0.11	
N. D.	4/10/34	6.85	4.29	2.56	1.68	0.42	1.25	0.59	0.30	50
C. H.	10/23/34	7.17	4.61	2.56	1.85	0.45		1.86	0.25	20
H. M.	9/18/34	7.58	4.63	2.95	1.59	0.36	1.60	0.45	0.54	10
I. S.	6/ 5/34	6.54	4.08	2.46	1.66	0.56	1.08	0.56	0.26	15
S. B.	3/ 6/34	7.29	4.26	3.03	1.40	0.46	1.44	0.62	0.43	31
M. S.	4/16/35	6.60	4.34	2.26	1.92	0.32	1.19	0.54	0.21	10
A. S.	1/ 8/35	7.38	4.90	2.48	1.92	0.28	1.26	0.48	0.46	25
K. Z.	3/20/34	7.25	4.54	2.71	1.67	0.26	1.14	0.69	0.62	85
Average		7.02	4.42	2.60	1.71	0.33	1.32	0.54	0.39	30

TABLE IV

RHEUMATOID ARTHRITIS (CHRONIC INFECTIOUS ARTHRITIS)	HYPERTROPHIC ARTHRITIS (OSTEOARTHRITIS)
Atrophic arthritis	Degenerative arthritis
Proliferative arthritis	
Primary progressive polyarthritis	
HISTORY	HISTORY
Sometimes present in family	Rarely present in family
Rheumatic fever at times	No rheumatic fever
Colds, sore throats, sinusitis	Unimportant
Indigestion	Unimportant
Underweight, undernourished	Overweight
Occasionally slight fever	No fever
Focus often present	Focus rarely present
<i>Joints first involved</i>	<i>Joints first involved</i>
Smaller joints of hands, elbows, knees, shoulders, ankles	Weight-bearing joints { knees hips spine
	Distal phalangeal joints—so-called "Heberden's nodes"
<i>Type of development</i>	<i>Type of development</i>
Soft tissue with later destruction of cartilage and bone	Bony involvement with deposit of calcium
<i>X-ray findings</i>	<i>X-ray findings</i>
None early. Later, bone rarefaction, destruction, deformity and ankylosis.	Increased density and spurring
Muscular atrophy	No atrophy
Progress to deformity	Does not progress to deformity
Cardiac involvement in a small percentage	No cardiac involvement
<i>Extremities:</i> cold, often	<i>Extremities:</i> warm
Often present: { Hypertrichosis Psoriasis	Rarely present
Subcutaneous nodules in 20%	Never present
LABORATORY FINDINGS	LABORATORY FINDINGS
Often anemic	Rarely anemic
Slight leucocytosis, sometimes	No leucocytosis
Increased sedimentation rate	Normal sedimentation rate
<i>Streptococcus hemolyticus</i> agglutination	Never positive
sometimes positive	
Increased blood globulin	Normal globulin

tent as determined by Van Slyke and others.⁷ His average normal figures obtained were:

	MAXIMUM	MINIMUM
Total protein	7.5	5.6
Albumin	4.9	3.4
Globulin and fibrinogen	2.9	2.3
Albumin/globulin ratio	2.0	1.4

The results as obtained in 15 cases of severe atrophic (rheumatoid) arthritis and one case of rheumatic fever are given in Table II, while those obtained in 14 cases of hypertrophic arthritis are shown in Table III. Atrophic (rheumatoid) arthritis was differentiated clinically from hypertrophic arthritis on the basis of Table IV.

In Table V are given the results obtained from the study of the blood of six arrested cases. By arrested is meant those cases of long duration in which activity has practically ceased.

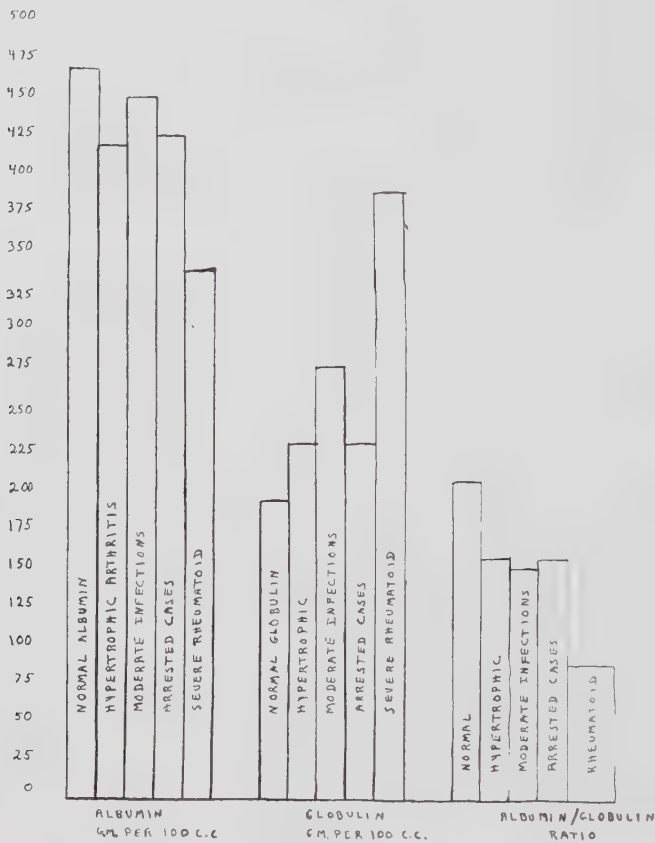
TABLE V
ARRESTED CASES OF ATROPHIC (RHEUMATOID) ARTHRITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
E. H.	9/11/34	7.13	3.94	3.19	1.24	0.61	1.37	0.63	0.58	45
M. C.	4/ 2/34	6.71	3.85	2.86	1.35	0.62	1.37	0.54	0.33	
M. P.	10/ 2/34	6.87	4.54	2.33	1.95	0.32	0.68	0.86	0.47	30
A. K.	5/ 8/34	7.68	4.92	2.76	1.78	0.28	1.47	0.62	0.39	28
S.	3/ 8/34	6.82	4.12	2.70	1.5	0.52	1.15	0.45	0.58	62
A. S.	5/ 8/34	7.41	4.43	2.98	1.48	0.38	1.57	0.58	0.45	50
F.	9/25/34	7.01	4.07	2.94	1.38	0.45	1.34	0.65	0.50	

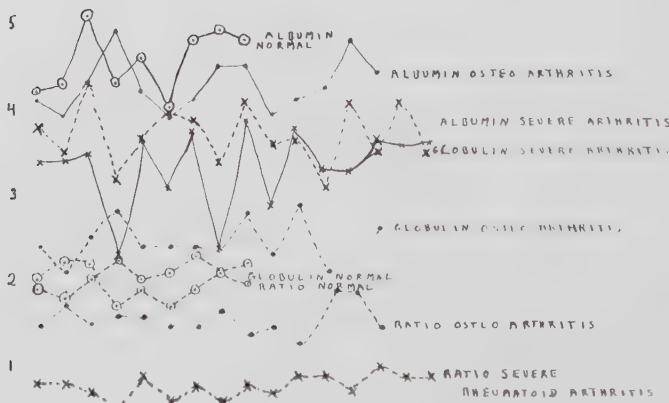
TABLE VI
MODERATE ATROPHIC (RHEUMATOID) ARTHRITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
G. K.	4/10/34	7.89	4.76	3.13	1.52	0.40	1.50	0.65	0.58	80
T.	4/ 3/34	6.91	4.32	2.59	1.66	0.50	1.38	0.50	0.21	
C.	11/20/34	7.07	3.85	3.22	1.20	0.55	1.54	0.85	0.28	25
L. I.	9/18/34	7.57	4.43	3.14	1.41	0.59	1.34	0.71	0.50	42
F.	11/ 3/34	7.62	4.27	3.35	1.27	0.64	1.62	0.51	0.58	
M.	4/17/34	7.27	4.08	3.19	1.28	0.52	1.75	0.44	0.48	
H.	9/25/34	7.08	4.53	2.55	1.78	0.45	1.46	0.38	0.26	20
C. R.	5/ 9/34	7.73	4.79	2.94	1.65	0.53	1.34	0.69	0.38	
E. H.	6/26/34	7.27	4.59	2.68	1.71	0.33	1.48	0.60	0.27	30
G. P.	6/12/34	7.25	3.82	3.43	1.11	0.47	1.58	0.66	0.72	
L. K.	6/19/34	7.57	4.40	3.17	1.39	0.29	1.68	0.62	0.58	45
F. S.	11/20/34	7.38	4.28	3.10	1.38	0.78	1.35	0.64	0.33	30
J. B.	10/23/34	8.05	4.91	3.14	1.56	0.86	2.06		0.22	35
G. K.	2/20/34	6.06	3.82	2.24	1.71	0.36	0.92	0.69	0.27	
J. B.	4/24/34	6.72	4.35	2.37	1.83	0.49	1.02	0.47	0.39	40
B. S.	3/13/34	7.41	4.28	3.13	1.37	0.31	1.82	0.68	0.32	
A. N.	5/29/34	7.03	3.86	3.17	1.21	0.61	1.43	0.54	0.59	15
H. P.	5/ 6/35	7.84	4.36	3.48	1.25	0.48	1.92	0.61	0.47	
A. H.	10/ 2/34	7.30	4.38	2.92	1.50	0.56	1.15	0.70	0.51	60
D. C.	5/14/35	7.42	4.62	2.80	1.65	0.32	1.39	0.62	0.47	
Average		7.32	4.33	2.98	1.47	0.51	1.46	0.61	0.42	38

The chemical changes which occur in the blood of 16 mild atrophic (rheumatoid) cases are shown in Table VI.



Graph 1.

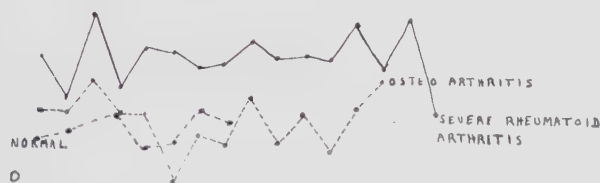


Graph 2.

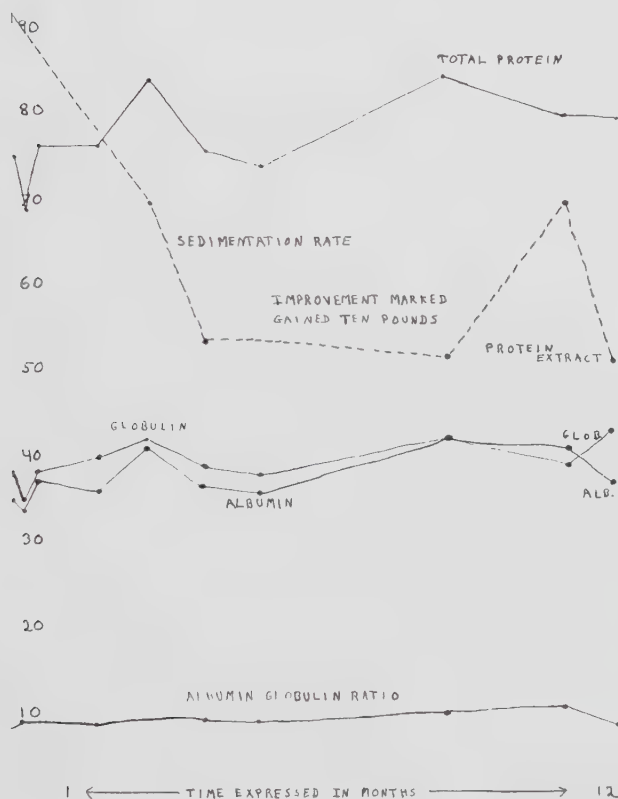
Graphs 1 and 2 are made from a summary of the albumin-globulin and albumin/globulin ratios given in Tables I, II, III, V, and VI.

In Graph 3 are shown the differences in the euglobulin fractions referred to above. It can be seen here that the greatest changes take place in the euglobulin fractions.

One patient, M. M., has been followed over a period of one year. She has a very severe atrophic (rheumatoid) arthritis which fluctuates considerably from time to time. The changes in her blood protein fractions, as well as in her



Graph 3.



Graph 4.

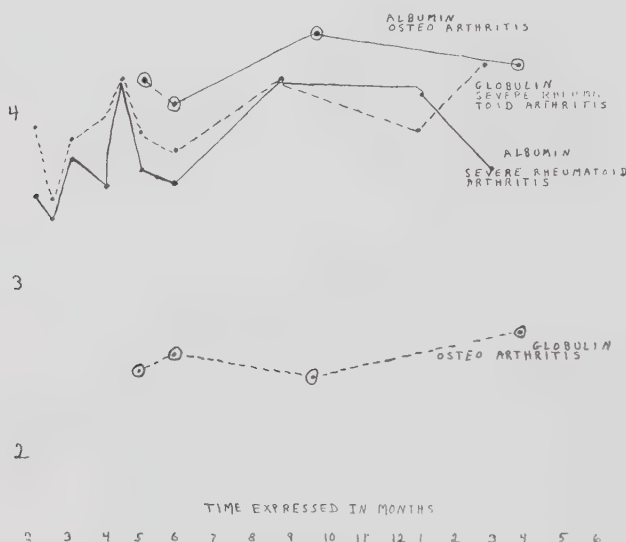
clinical course, are given in Table VII and Graph 4. The relationship between the plasma albumin and plasma globulin values of the blood of this patient M. M. and the patient E. O., ill with hypertrophic arthritis, is shown in Graph 5.

One patient, J. B., who made a complete recovery from a very acute and debilitating atrophic (rheumatoid) arthritis, was seen at weekly intervals during his illness and on three occasions his plasma proteins were determined.

These findings have been recorded in Table VIII. It is of interest that shortly after his recovery his albumin/globulin ratio had risen above the normal range. This has been noticed in one other patient, who made a sudden and complete recovery. It seems to be, as it were, an over-compensation which will later return to a normal level.

Three patients, J. J., B. K., and M. L., had very severe atrophic (rheumatoid) arthritis, associated with considerable edema. The plasma albumin in all three instances was quite low, as can be seen from a study of Table II. It is suggested that this lowering of plasma protein may play some part in the production of the edema and that perhaps a diet high in protein is advisable. Such experiments are now being made.

In Table IX are given a series of findings from the blood of patient E. O., ill with hypertrophic arthritis. This patient has shown little clinical change.



Graph 5.

O. F., a patient ill with severe atrophic (rheumatoid) arthritis, improved following a transfusion of whole blood, in addition to various other forms of treatment, but has recently become worse. The findings in his case are given in Table X.

H. I., a patient who had been crippled with rheumatoid arthritis for six years and whose disease was considered to be arrested, was progressively improving until recently, when she became acutely ill with bronchitis. During the illness her arthritis again became active. The changes which took place in her plasma protein are shown in Table XI.

In Table XII are given the findings obtained in five cases of myositis. These figures fall within the normal range.

In order to have controls in other pathologic states, the plasma proteins of six patients ill with other diseases were determined.

TABLE VII

A PATIENT WITH SEVERE ATROPHIC (RHEUMATOID) ARTHRITIS WHO SHOWED NO CHANGE OVER A PERIOD OF ONE YEAR

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE	REMARKS
M. M.	2/20/34	7.54	3.56	3.98	0.90	0.68	1.89	0.66	0.75	92	Put on high protein diet. Extensive involvement
	2/27/34	6.93	3.42	3.51	0.95	0.45	1.89	0.63	0.54		No change
	3/ 6/34	7.65	3.79	3.86	0.98	0.55	1.95	0.60	0.76		Feels better
	4/ 3/34	7.65	3.64	4.01	0.91	0.81	1.91	0.63	0.66		Feels fairly well
	4/24/34	8.41	4.17	4.24	0.98	0.63	1.94	0.65	1.02	70	Has been taking protein for 1 month. Is improved
	5/15/34	7.61	3.70	3.91	0.95	0.48	1.67	0.68	1.08	55	About the same. Gained 2 pounds
	6/12/34	7.44	3.61	3.83	0.94	0.50	1.84	0.58	0.81	55	Not so well. Pulse rapid. Heart both-ering
	9/18/34	8.42	4.21	4.21	1.00	0.53	1.90	0.53	1.25	48	Gained 7 pounds. Feels pretty well
	1/ 8/35	8.11	4.16	3.95	1.05	0.39	1.66	0.80	1.10	70	Gained 2 pounds. Taking protein
	3/12/35	8.08	3.74	4.34	0.87	0.64	2.00	0.73	0.97	55	No protein in 6 weeks. Hands, knees, ankles swollen

TABLE VIII

A CASE OF MODERATE ATROPHIC (RHEUMATOID) ARTHRITIS WITH COMPLETE RECOVERY

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
J. B.	10/23/34	8.05	4.91	3.14	1.56	0.86		2.06	0.22	35
	12/ 8/34	7.23	4.94	2.29	2.16	0.40	1.12	0.34	0.43	5
	3/19/35	6.94	4.97	1.97	2.52	0.24	0.85	0.61	0.27	

TABLE IX

CASE OF HYPERTROPHIC ARTHRITIS SHOWING NO CLINICAL CHANGE

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE	REMARKS
E. O.	5/ 1/34	6.76	4.25	2.51	1.69	0.20	1.30	0.57	0.44	5	Pain in knees. Heberden's nodes
	6/19/34	6.73	4.12	2.61	1.57	0.40	1.36	0.49	0.36	20	Omnidin, 1 amp. weekly
	10/ 2/34	7.04	4.55	2.49	1.83	0.16	1.37	0.74	0.22		No change
	4/16/35	7.07	4.32	2.75	1.57	0.56	1.28	0.54	0.37	25	No change

From Table XIII it can be seen that changes occur in other diseases similar to those which occur in atrophic (rheumatoid) arthritis, but perhaps not quite so marked. It is also of interest that in the case of liver disease studied here, the fibrinogen rise is out of proportion to the other blood changes.

Eleven months after the plasma protein determinations had been made, on normal subject J. D., he developed mumps, which was followed by a painful virus arthritis involving shoulders, wrists, and one knee. During the second week of this arthritic attack, his plasma protein was again taken. The changes which occurred are shown in Table XIV.

TABLE X

VARIATIONS IN PLASMA PROTEIN IN A CASE OF SEVERE ATROPHIC (RHEUMATOID) ARTHRITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE	REMARKS
O. F.	3/ 2/34	7.75	3.89	3.86	1.01	0.57	2.49		0.80	97	Considerable involvement
	5/ 9/34	7.08	3.81	3.27	1.16	0.40					High protein intake
	5/18/34	7.74	4.17	3.57	1.14					80	Improving
	6/21/34	7.39	4.11	3.28	1.25	0.54	1.48	0.65	0.61	80	Improving
	7/ 2/34	7.41	4.37	3.04	1.44	0.52	1.28	0.47	0.77		Much improved
	10/16/34	7.80	3.78	4.02	0.94	0.70	1.58	0.79	0.95		Marked swelling
	4/15/35	7.41	3.81	3.60	1.06	0.71	1.65	0.66	0.58		Quite bad. Receiving typhoid vaccine intravenously

TABLE XI

A CASE OF ARRESTED ARTHRITIS BECOMING ACTIVE AFTER "GRIPPE"

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE	REMARKS
H. S.	3/20/34	7.08	4.12	2.96	1.39	0.46	1.37	0.69	0.44	0.53	
	5/ 8/34	7.41	4.43	2.98	1.48	0.38	1.57	0.58	0.45	0.50	
	6/ 5/34	7.29	4.34	2.95	1.41	0.37	1.50	0.62	0.46	0.25	
	6/26/34	6.90	4.22	2.68	1.57	0.31	1.37	0.46	0.54	0.30	Improved
	9/11/34	6.61	3.69	2.92	1.26	0.48	1.29	0.67	0.48	0.30	Bronchitis
	5/15/35	6.92	3.62	3.30	1.10	0.50	1.46	0.62	0.72		

TABLE XII

MYOSITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE
L. L.	9/25/34	7.74	5.18	2.56	2.02	0.38	1.26	0.59	0.33	15
H. F.	4/10/34	7.26	4.55	2.71	1.68	0.50	1.43	0.47	0.31	15
H. C.	12/18/34	6.58	4.43	2.15	2.06	0.17				3
C. G.	4/16/35	6.45	4.27	2.18	1.95	0.40	1.01	0.55	0.22	
C. L.	10/16/34	6.83	4.51	2.32	1.94	0.52	1.08	0.48	0.24	
E. H.	9/25/34	7.08	4.53	2.55	1.78	0.45	1.46	0.38	0.26	

DISCUSSION

A number of investigations^{8, 9} have shown that there is a rise in globulin and a fall in albumin in certain febrile diseases. Moen and Reimann¹⁰ have shown that this change is rather marked in lobar pneumonia. It has also been

suggested¹¹ that the rise in globulin is in a way an immunologic reaction and that the species of globulin varies with the disease.¹²

Epstein,¹³ Van Slyke¹⁴ and others have demonstrated that in certain renal diseases, edema is associated with a lowering of plasma albumin and sometimes with plasma globulin and that in such cases restriction of protein is dangerous. Peters and Van Slyke¹⁵ state "that the deficit following either proteinuria or

TABLE XIII
PLASMA PROTEIN FINDINGS IN DISEASES OTHER THAN ARTHRITIS

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.	SED. RATE	REMARKS
E. B.	1/ 5/35	7.16	3.74	3.42	1.09	0.33	1.93	0.67	0.49	10	Central nervous system syphilis. An- eurysm
T. P.	4/12/34	6.24	3.81	2.43	1.57	0.48	1.00	0.51	0.44	24	Paralysis agitans 7 years
P. R.	5/ 3/34	5.65	4.01	1.64	2.44	0.21	0.99	0.25	0.19		Severe urticaria. Ad- renalin adminis- tered; very re- stricted diet
K. C.	4/22/35	7.23	4.26	2.97	1.43	0.70	1.18	0.70	0.39	60	Tumor of liver
U. M.	4/ 9/35	6.26	3.41	2.85	1.20	0.45	1.12	0.72	0.56		Acute cholecystitis
A. D.	1/10/35	7.49	4.49	3.00	1.50	0.27	1.45	0.73	0.55		Pernicious anemia

TABLE XIV
BLOOD PROTEIN CHANGES IN ACUTE ARTHRITIS OF SHORT DURATION

NAME	DATE	TOTAL PROT.	ALB.	GLOB.	RATIO	FIBRIN.	PSEUDO I	PSEUDO II	EUGLOB.
J. D.	3/12/34	6.40	4.18	2.22	1.88	0.30	1.32	0.40	0.20
	2/11/35	5.98	3.35	2.63	1.27	0.42	1.24	0.53	0.44

malnutrition falls, as a rule, chiefly on the albumin fractions and is accompanied by a tendency to edema. The edema of degenerative Bright's disease appears certainly and edema of various malnutrition states probably to be due to albumin deficit in blood plasma."

In the light of this knowledge, our findings would suggest that atrophic (rheumatoid) arthritis is an infectious disease, possibly associated with malnutrition, while hypertrophic arthritis is not, for in atrophic (rheumatoid) arthritis is found a lowered plasma albumin and an increase in plasma globulin. The major increase takes place in the euglobulin fraction. There is little or no change in the plasma protein in hypertrophic arthritis.

Furthermore, in certain cases of atrophic (rheumatoid) arthritis, particularly those associated with easily demonstrable edema, it seems unwise to restrict protein in the diet. It has been said that protein will remove fluid from the tissue, because it takes fluid to excrete the protein. Such is not the case with carbohydrate. Pemberton¹⁶ has demonstrated water retention in individuals on high carbohydrate diets,

As in other infectious diseases, the plasma protein in the patient ill with atrophic (rheumatoid) arthritis tends to return to a normal level as the patient recovers.

There is also an increase in fibrinogen in the blood of the atrophic (rheumatoid) arthritic patient. Usually when the fibrogen is highest the globulin rises the least.

The sedimentation rate is a rough way of determining whether there is a rise in plasma globulin, or fibrinogen, or both, provided there is no marked change in cell volumes.

CONCLUSIONS

1. Globulin fraction tends to rise in atrophic (rheumatoid) arthritis.
2. The greatest change takes place in the euglobulin fraction.
3. Albumin tends to fall in atrophic (rheumatoid) arthritis.
4. There is little, if any, change in the protein fraction of those ill with hypertrophic arthritis.
5. Further evidence is presented to show that atrophic (rheumatoid) arthritis is an infectious disease, while hypertrophic arthritis is not.
6. The sedimentation rate is a simple way of determining in a rough manner whether there has been a change in the globulin or fibrinogen, or both, providing a correction is made for the cell volume.
7. Theoretically, a diminished sedimentation rate is not always an accurate index of improvement as accomplished by vaccine, for a rise in globulin has been produced by certain vaccines and this per se might increase the sedimentation rate. This has not been our experience in using hemolytic streptococcus vaccine.
8. Fibrinogen content usually rises in atrophic (rheumatoid) arthritis but not in proportion to the globulin rise.
9. Restriction of protein in the diet of the atrophic (rheumatoid) arthritic patient might at times be dangerous.
10. Vitamin deficiency and malnutrition may play a part in the protein changes in atrophic (rheumatoid) arthritis.

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DISCUSSION

DR. RALPH PEMBERTON, PHILADELPHIA, PA.—I am chiefly interested in Dr. Davis' report, for two reasons, because of the implications it bears toward the nutritional aspects of chronic arthritis, and because Dr. Scull, working in our laboratory, met with somewhat comparable figures about a year ago in a series of fourteen cases. The figures we obtained are not so striking as those Dr. Davis reports but they are not out of line with his and suggest that it may be worth while for us to take the matter up again and pursue it further.

Dr. Davis' observations are also in line with the suspicion raised in the minds of Dr. Scull and myself as to the existence of what, for want of a better term, we have called a low-grade "edema" in many cases of chronic arthritis of both types.

Another phase of Dr. Davis' work which is of interest is the fact that he found the same albumin-globulin ratio in arrested cases of atrophic arthritis as he found in cases of hypertrophic arthritis, which is highly suggestive. As pointed out earlier today by Dr. Haden, deviations of this nature may well have an important significance.

Caution should be exercised in interpreting observations of this sort, as in interpreting the significance of agglutination reactions in arthritis, but it appears that Dr. Davis has opened wider a window looking out upon important phases of the problem which need to be explored further.

DR. RALPH H. BOOTS, NEW YORK, N. Y.—Dr. Davis seems to offer an explanation for the increased sedimentation rate in severe cases of atrophic (rheumatoid) arthritis. He finds a rise in the globulin fraction and a fall in the albumin fraction. If one accepts Dr. Snapper's explanation of the factors influencing sedimentation rates, the rise in globulin fraction could explain the rapid sedimentation rate in these cases. Furthermore, the increase in the euglobulin fraction indicates that it may be the result of infection. He finds the euglobulin fraction normal in cases of hypertrophic arthritis, which coincides with the belief that these are of degenerative nature. I believe this is the first work of its kind in these two arthritic diseases. It would be interesting to see the results of similar determinations in gout; here we have increased sedimentation rate in cases we believe not to be due to infection.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—Certain therapeutic implications are suggested by this paper: In certain types of edema there are definite alterations in the albumin and globulin ratios, and a distinct diminution in total plasma protein; and following the taking of a high protein diet there is sometimes a disappearance of edema with the establishment of normal blood proteins. Has Dr. Davis pursued his studies far enough to determine whether similar dietetic procedures are beneficial in patients with chronic arthritis?

DR. RUSSELL L. HADEN, CLEVELAND, O.—I would like to emphasize the importance of Dr. Davis' work, in relation to the occurrence of edema in chronic atrophic arthritis. The important point so far as edema is concerned is the relation between albumin and globulin in the blood plasma. With such changes as Dr. Davis describes there is necessarily a lessened osmotic pressure of the blood proteins and so an increased tendency to the development of edema. As Dr. Boots has said, this might be urged as proof that chronic atrophic arthritis

is infectious in type. I have been interested in the relation of albumin to globulin in thyroid disease. In hyperthyroidism, presumably not due to infection, our findings are almost identical with those reported by Dr. Davis for atrophic arthritis.

DR. S. C. WOLDENBERG, WASHINGTON, D. C.—In the past three years we have run in the Veterans' Hospital at the Bronx, N. Y., over 300 cases of hypertrophic arthritis, and we have found that many of the patients have a normal sedimentation rate. Three weeks later some of these patients had bronchitis or other respiratory conditions; the sedimentation rate was then increased. It has been stated by some that an altered sedimentation rate is an indication for sulphur therapy in the treatment of arthritis.

It may be of interest to state that we have studied the amino acid content of blood in 27 cases of arthritis and have found none of them deficient in any of the amino acids, except the cystine.

DR. DAVIS, JR. (closing).—In answer to Dr. Swift's question, we have done some urinary studies to see if there was an albuminuria that would account for the fall in albumin in the plasma. I have not done enough to really say. I have given a number of these patients a very high protein intake. It does not harm them and several have been benefited. We are working on that line now to see if it has some relation to the change in the albumin fraction.

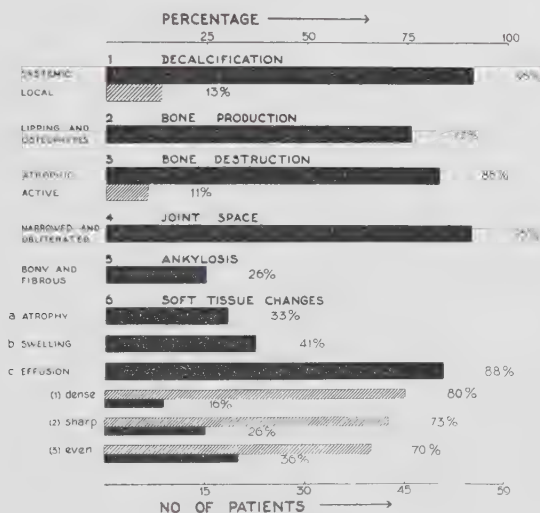
A STUDY OF THE ROENTGENOLOGIC FINDINGS IN VARIOUS TYPES OF CHRONIC ARTHRITIS

ABSTRACT

G. DOUGLAS TAYLOR, M.D., A. B. FERGUSON, M.D., HAIG KASABACH, M.D.,
AND M. H. DAWSON, M.D., NEW YORK, N. Y.

TO CORRELATE the clinical and roentgenologic findings in various forms of chronic arthritis, 163 cases have been studied: 52 of rheumatoid arthritis, 32 of osteo-arthritis, 12 of gout, 11 of gonorrheal arthritis, 32 of tuberculous arthritis, 12 of Marie-Strümpell spondylitis, and 12 of Still's disease.

TABLE I RHEUMATOID ARTHRITIS



Among the special roentgenologic characteristics studied were systemic, regional, and local decalcifications; production of bone, lipping and osteophytes; active and atrophic destruction of bone; narrowing of joint spaces; bony or fibrous ankylosis; and atrophy, swelling or effusion as indicated by soft tissue shadows. No single roentgenologic feature is diagnostic for any one type, as the majority of these alterations are common to all types of chronic arthritis, but each type tends to present a characteristic combination of findings that constitutes its own pattern. It may be necessary to examine more than one articular region to find these characteristics, and it is recommended that the hands, feet, knees, and lumbar spine be routinely examined by roentgenograms, regardless of the joints of which the patient complains.

A study of soft tissue shadows, frequently overlooked, is of utmost importance in the differential diagnosis. Roentgenograms may show little or no change in the early stages of rheumatoid, osteo-, gouty, or tuberculous arthritis or Marie-Strümpell spondylitis. In the early stages of gonorrheal

TABLE II OSTEO-ARTHRITIS

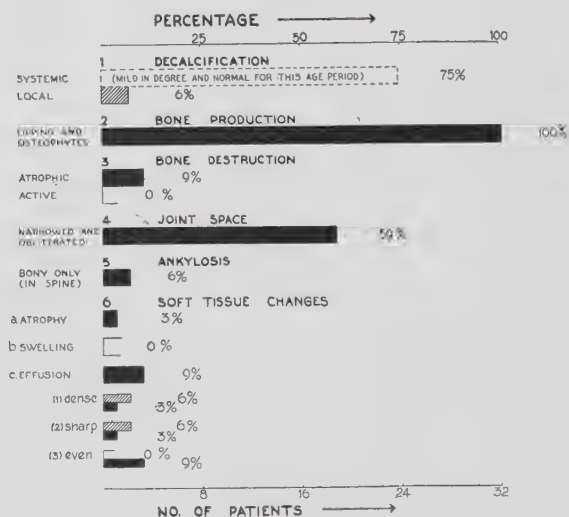
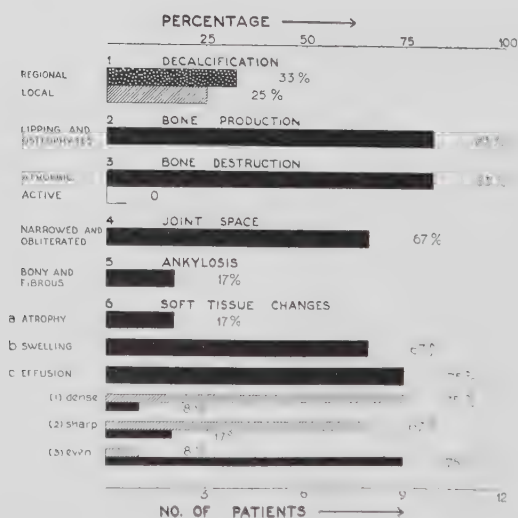


TABLE III GOUT



arthritis, however, roentgenograms are frequently of the greatest assistance in diagnosis. The roentgenologist should be told at least the duration and severity of the joint symptoms in order to make a rational interpretation of the roentgenographic shadows. The appearance of a gonococcal arthritis of six weeks' duration may closely resemble that of a tuberculous joint of six months' duration.

Our roentgenologic studies indicate that rheumatoid arthritis and osteoarthritis are distinct entities. Rheumatoid arthritis cannot be divided into subgroups by roentgenologic examination. Rheumatoid arthritis, Still's disease, and Marie-Strümpell spondylitis present the same characteristic group-

TABLE IV GONOCOCCAL ARTHRITIS

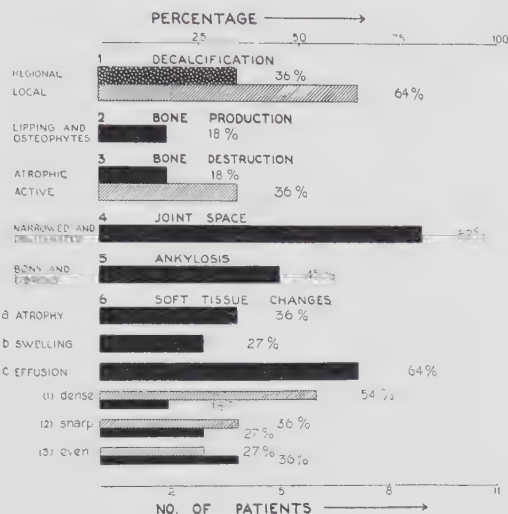
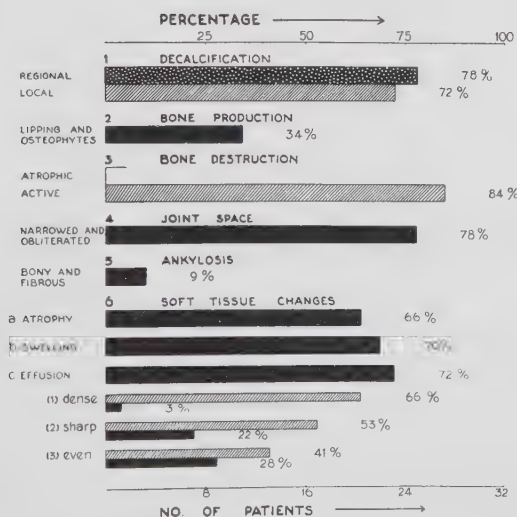


TABLE V TUBERCULOUS ARTHRITIS



ing of the roentgenologic findings, a correlation which supports the clinical conception of the three processes being different manifestations of the same disease. Marie-Strümpell spondylitis and hypertrophic spondylitis (osteoarthritis of the spine) present distinct and different roentgenologic appearances. Localized areas of atrophic destruction of bone ("punched-out areas")

are seen as frequently in cases of atrophic arthritis as in gout. Roentgenograms properly interpreted are a most valuable aid in the differential diagnosis and prognosis of the various types of chronic arthritis.

TABLE VI MARIE-STUMPPELL ARTHRITIS

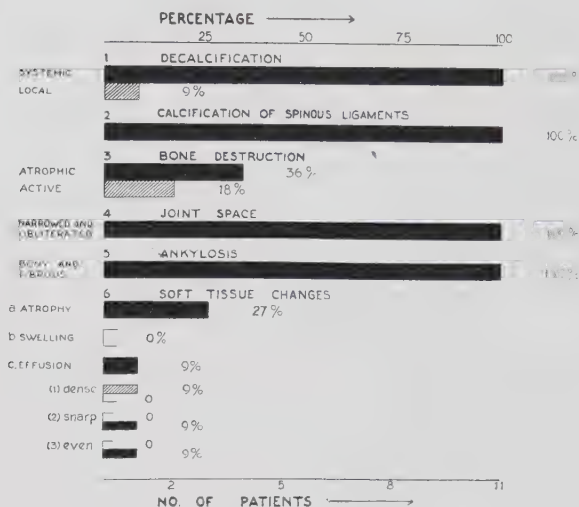
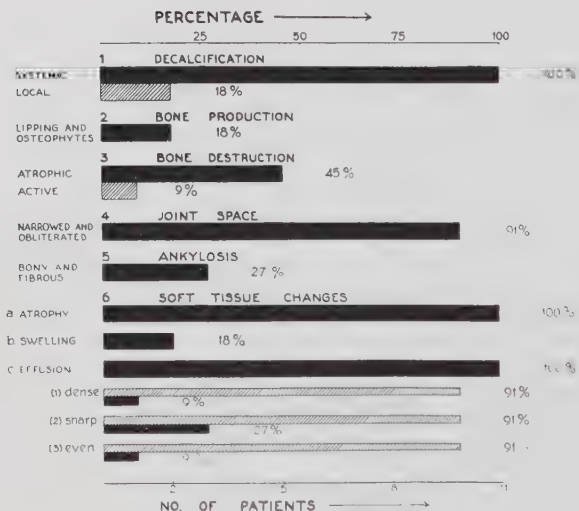


TABLE VII STILLS' DISEASE



DISCUSSION

DR. JOHN G. KUHN, BOSTON, MASS.—This careful study of the roentgenologic findings in various forms of chronic arthritis is most commendable, but all such groupings of characteristic alterations in roentgenograms have definite limitations. While the typical patterns described are seen in the majority of cases at certain stages of the disease, the roentgenologic changes of the joints and their surrounding structures can be modified greatly by repair of the pathologic changes, by a return to something approaching normal function of the joint, and, to a lesser extent, by a diet rich in minerals required in bone

formation. The apparent effusions described by the authors are often simply capsular and synovial thickenings, as operations have repeatedly demonstrated. In roentgenograms they are frequently indistinguishable from effusions. I have been unable to differentiate between the calcaneal spurs seen in gonorrheal infections and those found in cases in which faulty statics of the lower extremity is apparently the only cause. With the other findings we are in entire agreement.

DR. A. B. FERGUSON, NEW YORK, N.Y.—May I enlarge on some of the roentgenologic features brought out by Dr. Taylor. We studied forty-nine roentgenologic characters. Each one had a particular meaning to us. Our greatest difficulty is in carrying that meaning over to you. Each term we used has a technical roentgenologic meaning. For instance, the word effusion as used by us covers whatever is within the capsule, whether free material, granulations, or anything else. They all cast the same shadow roentgenologically. May I clarify our meaning about a few things: First, decalcification. Bones become less calcified with age. That is what is seen in hypertrophic arthritis (degenerative arthritis or osteo-arthritis). When we speak of an abnormal systemic decalcification, we mean that the decalcification is not commensurate with the patient's age. In fact, we have made a roentgenologic diagnosis of degenerative arthritis in a case in which the patient was twenty-eight years of age, solely because of the decalcification in the hands and feet. Local decalcification is a circumscribed decalcification limited to some particular portion of the bones or to a group of small bones, such as those of the wrist. Soft tissue shadows are not analyzed sufficiently in roentgenologic literature. It is noted that some mass of soft tissue, which is called swelling or effusion, is present, but the detailed characteristics of its appearance and distribution are not studied. Their consideration is of importance because it is the character of these early changes in the soft tissue which enables one to recognize early lesions in cases in which there are no other changes. The characteristic outline of the swellings of the soft tissues and their distribution should be noted. When one considers a certain feature as typical of a disease, one implies that in any case of that disease, the roentgenographic appearance of some joint should conform to that particular finding, even though the appearance of other joints differs. In cases of rheumatoid arthritis there may, for example, be a high percentage of bone production, or lipping, but this may not be a typical feature of the disease. Lipping at the great toe may have nothing to do with rheumatoid arthritis. I believe that the feet, hands, and knee joints should be examined roentgenographically in every case of obscure arthritis regardless of the joint affected, in order to obtain a general view of the constitutional changes produced by the disease.

DR. JOSEPH A. FREIBERG, CINCINNATI, OHIO.—The impression that roentgenograms show punched-out areas of bone in early as well as in advanced cases of gout is not true. It is important to remember that patients with mild or even moderately severe gout may show no roentgenologic changes whatsoever.

DR. J. A. KEY, ST. LOUIS, Mo.—I am glad to see roentgenologists paying attention to swelling of soft tissue and hope they will be able to differentiate between various types of swelling. Swellings of soft tissue are the first evidences of disease in joints and may be present when the bones appear normal. The more I study roentgenograms, the more I need to know about the clinical history of the case. Phemister showed that narrowing of the joint space was a late finding in tuberculous arthritis because the bearing surface of the cartilage is not absorbed, while in acute arthritis it is absorbed early. In gout, the punched-out areas are the result of subchondral deposits in the bone. In acute arthritis and gonorrheal arthritis the punched-out areas are caused by erosion of the cortex of the bone. They occur around the margins of the cartilage and are the result of invasion by the diseased tissue. In considering atrophic bone one should know the duration of the abnormal state and how much circulatory change has been present during that time. Any process which increases the circulation and local heat will cause atrophy of bone. Last, one should know how much strain the bone has been subjected to, because lack of function from immobilization or from pain may explain the atrophy.

DR. RALPH PEMBERTON, PHILADELPHIA, PA.—At the risk of appearing somewhat divergent, I would like to call attention to the importance of extending, to a greater extent than now exists, a better knowledge of the gross morbid anatomy of arthritis to the various groups of surgical and other specialists who are working on the fringe of the arthritic problem. Without any reflection on the excellent paper which we have just heard, this desideratum is perhaps nowhere more important than in the field of radiology. A considerable experience has taught me that most radiologists who see an overgrowth of bone make a diagnosis of "hypertrophic arthritis," and if overgrowth is absent the diagnosis becomes "atrophic arthritis." The time has come for a more informed type of scrutiny. There are about 200 of us here today who will shortly return to our respective places of work. I hope that representations will be made by all of us that a demand exists for fuller knowledge of the pathology of the disease on the part of those whose activities touch the arthritic syndrome.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—What do the authors consider the minimal number of roentgenograms which would be required to make a correct differential diagnosis?

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—In what percentage of cases is the roentgenologic diagnosis in accord with that based on clinical, bacteriologic, and other laboratory findings? Have any roentgenologic changes been found in joints involved in rheumatic fever, especially in those joints in which there has been long-continued effusion? Can a gonorrheal arthritis be distinguished roentgenologically from ordinary septic arthritis? In what percentage of joints examined roentgenologically can a definite diagnosis be made?

DR. M. H. DAWSON, NEW YORK, N. Y.—I feel that roentgenologic diagnosis is just as reliable, if not more so, than the clinical diagnosis of the arthritis.

DR. G. DOUGLAS TAYLOR, NEW YORK, N. Y.—The diagnoses and analyses of the two roentgenologists, Drs. Ferguson and Kasabach, were made without either of them knowing anything about the clinical histories. We made separate clinical studies, presented the roentgenograms to them, and checked their reports. We then checked the cases by various clinical and laboratory methods. In the Presbyterian Hospital, Drs. Dawson and Boots studied the cases. In the New York Orthopedic Hospital, postoperative examination of sections was made in most of the cases. Consequently, we thought we could defy anyone who disputed the diagnosis in what we called "typical cases." We found that the roentgenologic diagnosis in these "typical" cases agreed with the clinical diagnosis.

The roentgenologists were told the duration of the symptoms, the severity of the disease, and whether the joints had been used, or whether function had been interfered with. We found "punched-out" areas of atrophic bone destruction just as frequently in cases of atrophic arthritis as we did in cases of gout. We agree with Dr. Freiberg that in early gout there may be little or no change in the roentgenograms. In this study we included only the more advanced cases of gout.

HOME TREATMENT OF CHRONIC ARTHRITIS BY PHYSICAL THERAPY

JOHN S. COULTER, M.D., CHICAGO, ILL.

NO PROGRAM for the treatment of chronic arthritis can be considered complete unless physical therapy is used. The best physical agents are obtained easily, i.e., heat, water, massage, physiologic rest, and exercise. These are used as adjuncts to other forms of treatment. Under direct observation the capillaries of the patients suffering from chronic arthritis show a markedly diminished peripheral blood flow. The therapeutic value of heat, massage, and exercise is to increase blood flow. Therefore it would seem a waste of the patient's time and money to limit physical therapy to one hour three times a week. If physical agents are used, they should be prescribed definitely by the physician. The patient and some member of the family should be instructed in their use at home. Thus the physician can secure for these patients somewhat the same treatment with physical therapy at home that they would get in a hospital or sanitarium, resulting in a considerable reduction in the cost of medical care for the patient and also helping the physician to keep control of the patient over the long period necessary for treatment.

The detailed procedure to be followed, as well as the objectives to be attained, should be carefully explained by the physician during the first visit to the patient. This is quite essential to secure the necessary intelligent cooperation. Usually the patient is shown that in the *Primer on Chronic Arthritis* issued by your association there are eight headings under treatment, and that physical therapy is an adjunct under six of these divisions. Then the use of each physical agent is carefully explained.

EXERCISE

This program is always started with a careful explanation of and a prescription for body mechanic exercises, because it is believed that a most important part of the treatment is to remove mechanical handicaps and to maintain the best possible body mechanics.

The following statement by Osgood¹ is read and explained to the patient in detail: "Atrophic arthritis is much more common in the young, thin, ptotic type of person. The 'set up' is inefficient. Their muscles are poor, their thoracic cages are narrowed, their diaphragmatic excursion is small, their abdominal viscera are sagged, the weight-bearing lines of their joints are not true, muscle tonus is hard to maintain because the center of gravity is disturbed. They are fatigued. Their body mechanics is wretched. If bad body mechanics can be converted into good body mechanics; if inefficient 'set ups' can be changed into efficient ones by positional rest periods, exercises, and temporary supports; if more room can be provided in the thoracic cage for heart and lung action; if the diaphragmatic pump can be set working again on the abdominal veins and viscera; if their symptomatic joints can have their normal weight-bearing thrusts

restored; then there would seem to be inevitably less wear and tear, a higher circulatory coefficient, more nearly normal alimentation, less fatigue and a better chance for the defense mechanisms of the body to overcome whatever bacterial or chemical toxins are being elaborated, which presumably are or will be responsible for the symptoms in the joints.

"In hypertrophic arthritis, the same principles of improving faulty body mechanics obtain. With its older age incidence, the remodeling of the body mechanics is harder but, fortunately, there is usually less remodeling to be done." The patient is often asked to read certain indicated parts of the recent book *Body Mechanics* by Goldthwait and others.²

The patient and some interested member of the family are instructed in the use of body mechanic exercises. The instructions are on mimeographed sheets. These exercises are based on the development of a firm, flat lower abdomen. The position desired is standing so that the weight falls well forward on the outer borders of the feet, the lower abdomen pulled in and up, the back flat, the head up, and chin in. The body should be stretched tall, without being rigid: the shoulders and chest will then fall into their own balance line. The physician should direct carefully and check over the performance of these exercises every week, adding new ones and leaving off the easier ones as the patient improves.

For local joint conditions during the acute stage, deformity must be prevented by rest in proper supports, but painless active motion is encouraged. These joints should never be manipulated by passive exercise, for swelling interferes with the circulation which is already poor and the diseased tissues are traumatized. During the subacute stage there are several forms of exercise that eliminate the weight of the extremity during movement and are helpful in allowing the patient to translate even minimal muscle power into active motion. In Gaenslen's sling suspension method the patient can exercise frequently for brief periods in the pain-free range. With a homemade tank in the average home the buoyancy of the water eliminates gravity and the warmth of the water relaxes the muscles and accelerates the blood flow.

After the acute and subacute stages have passed, free and resistive exercises are given on prescription by the physician. There should be a mimeographed sheet of exercises to be used for each joint. The best result in the restoration of function in stiff joints following chronic arthritis is not from manipulation but from the gradual use of these joints by directed exercise and occupational therapy.

In certain cases exercise apparatus is useful. Directions may be obtained for the construction of stall bars for arm and leg exercises, a shoulder wheel and abduction ladder, a Kanavel hand table, and stairs with rails for stair climbing exercise.

Rest and exercise are essential to the function of a joint. Motion should be encouraged in all stages of the disease, but this motion should be well within the fatigue limit.

Exercise for a single joint is monotonous. The human body is more than a machine and the formal repetition of a movement either with or without ap-

paratus is not of maximum therapeutic value in increasing the amount of movement in a stiff joint or as an integral part of a larger coordinated movement. There is no psychologic stimulant for personal incentive or sustained effort.

Occupational therapy may be applied at home under the direction of the physician and with the help of the family. It is inexpensive and very effective if the patient is willing to cooperate. For example, refinishing wooden furniture involves constant squatting and raising as the rungs of a chair and other parts are sandpapered and finished. This bending and straightening of the leg while at work offers exercise while the patient is thinking about his job. He is conscious not only of the exercise but is also inspired by his work. In working at home the patient and his family will take an interest in this form of exercise and during the events of the day will discover other normal tasks which will provide opportunity for the repetition of an exact motion. This is an important factor, for it does away with the more or less unconscious effort to save the affected part. Again definite directions will impress the patient with the surgeon's interest and repay the time taken in the functional restoration gained by the patient.

HEAT

Heat is applied locally over an arthritic joint to increase the local circulation. It has been shown that the quantity and quality of this heat must be prescribed by the physician. Landis³ has shown that the capillary pressure in the arterial side is 32 mm. mercury and 12 mm. in the venous end. This pressure rises to 60 and 45 mm. at a temperature of 42° C. Drury and Jones⁴ observed that edema formation is two to five times greater at 42° C. than at 16° C. Starr⁵ found that 30° to 35° C. were the best temperatures to secure an increase in circulation and relief of pain in circulatory disturbances of the extremities. Therefore it is believed that heat should be prescribed by the physician to secure a definite temperature for a stated period.

Bierman⁶ confirmed Sonne's work that during the applications of incandescent radiation of maximum tolerance the subdermal temperature at a depth of 0.5 cm. was 47.7° C., while with infra-red radiation at the same depth the temperature was 41.7° C. Therefore lamps which emit luminous and short infra-red rays are more effective to increase the temperature of the subcutaneous tissues than the ordinary infra-red generator which predominates in long infra-red rays. It is important for the physician to prescribe the kind of radiant heat to be applied.

The patient with chronic arthritis should be given directions for the local application of heat. A useful electric lamp baker can be made for about \$5.00.

Associated with massage, electrical muscle stimulation of the graduated contraction type is of great value. The excellent results are due to the direct stimulation of the muscles causing contractions as well as the mechanical effects due to the direct movement of the joint. It has been shown that these contractions are not followed by the production of lactic acid, as occurs when muscles are voluntarily contracted. Therefore muscular contraction of this kind partakes more of the nature of massage than it does of active exercise.⁷

An apparatus giving a sinusoidal faradic current has been devised that can be made for \$5.00. In certain cases this apparatus is sent home with the patient and instructions given to a member of the family in its use.

In addition to this local heat the application of heat systemically is of value. There has always been a popular belief in this application of heat for elimination, but Pemberton⁸ believes this value to be limited and not the only one. Some of the other effects are the increased circulation and metabolism induced. These effects are increased if following the general bake or bath a Scotch douche is given.

HYDROTHERAPY

In the use of water in the treatment of arthritis the Scotch douche and cold shower after a bake furnish a "metabolic and circulatory whip" if properly used. Where the proper apparatus is not available, a sheet bath is a valuable substitute. For home use again the patient should be given definite instructions for its use. For the generalized application of heat the hot bath may be used at home according to the directions given by Cecil.¹⁰

For local applications of heat by water a homemade whirlpool bath is often valuable. The whirling of the water under pressure and the air intake enable the water temperature to be increased to 110° and 120° F. The rapidly moving water and air bubbles also give an efficient form of gentle massage. Joint motion that could not otherwise be tolerated may be given while in the bath.

Contrast baths using hot water followed by cold are not used, as it has been noted by direct observation of the capillaries through the microscope that the capillary circulation is not increased by contrast baths as efficiently as with hot baths.

MASSAGE

There seems to be a deficient blood supply to arthritic joints. In the early stages of the disease when there are no joint signs and only intermittent joint symptoms, increasing the local blood supply to the joints by heat, massage and active exercise may restrain or prevent permanent tissue changes in the joint.

Pemberton⁸ has shown that the effect of massage in arthritis is to open vascular channels and increase the circulation. If this is so and there is a deficient circulation to these joints, it must follow that massage must be given at frequent intervals. For this reason we have our patients bring in some interested member of the family for instruction in the use of massage at home, as it is useless to give massage three times a week and no more. Every physician should be able to prescribe massage as he would drugs. It is dangerous to turn a patient with arthritis over to a technician with only directions to give massage. Heavy massage over an arthritic joint may cause a marked local reaction. An arthritic case should have gentle kneading massage above and below the affected joint and no massage over an acute joint. When the joint becomes subacute, superficial stroking massage may be started over the joint in addition to the kneading massage above and below the joint. This should be preceded by at least fifteen minutes of heat. Massage should be given for about ten minutes twice daily. The details of the technic of massage are given in the *Handbook of Physical Therapy*.

REST

If chronic fatigue is one of the chief factors in all arthritis, certainly rest is one of the most important agents in the treatment of the disease. Swaim and Kuhns⁹ state that fatigue is not only a subjective symptom but the physical signs of it are also present, for example, subnormal morning temperature, poor pulse, vasomotor instability, low blood pressure, lowered metabolism and poor muscle tone. They believe that fatigue of this kind is due to disturbances of the normal physiology of the organs in the thorax and abdomen, and has its effects chiefly through the circulation and sympathetic nervous systems as is shown by cyanosis of the lips, cold hands and feet, localized blanching, skin changes, and deranged heart action.

Rest should be prescribed with as much discrimination as any drug. Usually the rest should be in bed for certain periods daily or continuously. At first, after each meal a pillow is placed under the shoulders, the hands are placed under the head, and a pillow is placed under the knees. This raises the chest and abdomen, hyperextends the dorsal spine, and results in abdominal breathing with better use of the diaphragm.

After a half hour the face prone position is taken and radiant heat is applied to the spine to stimulate spinal circulation. These periods are given after meals whether the patient is in bed continuously or is ambulatory. If continuously in bed these periods are continued until exercises and proper supports enable the patient to continue this correct position when up. They are then allowed up for increasing periods.

Rest is also an important agent in the local treatment of the affected joints. Rest and exercise are most important in the function of a joint. This rest should be in a position best adopted to prevent strain or contracture, thus preventing deformities. These positions have been described by Swaim and Kuhns.⁹ The prescription of local rest illustrates the necessity of having the cooperation of an orthopedic surgeon in the treatment of chronic arthritis with physical therapy.

CONCLUSIONS

In chronic arthritis sufficient time for adequate treatment is fundamental, and physical therapy is an important adjunct in treatment. These physical agents can be used by any physician in any place, as they are cheap and easily obtainable, but to secure the best results they must be carefully prescribed and used under the physician's directions, not only in the hospital and office but also for longer periods at home by the patient assisted by some member of the family.

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DISCUSSION

DR. FRANK R. OBER, BOSTON, MASS.—Hospital physiotherapy under our present set-up for managing arthritic patients is impossible, since there are too many patients who have arthritis and not enough hospital beds to care for them. We have no mechanism whereby home treatment may be given, and there are not enough physiotherapists at present to instruct members of the family. Furthermore, very few physiotherapists are interested in treating arthritic patients and the average practitioner does not know enough about physiotherapy to carry out a well-balanced plan. In Massachusetts about 70,000 people suffering from arthritis receive no treatment whatever.

Under present conditions, the management of acute joints by home treatment is a dangerous occupation for either the physiotherapist or the family doctor. These arthritic patients must be handled very carefully. The doctor should understand how much exercise is necessary to promote the function of their joints. If they are to be badly treated, it would be wiser to let them alone. I do not believe anyone in the home can be instructed in the proper use of electricity, and it is doubtful in my mind if electricity has any great value. Many people think heat, electricity, and massage are going to work a miracle. These are only a very small part of treatment. If it comes to a choice between heat, electricity, massage, and exercise, throw the first three out of the window and use exercise.

The program which Dr. Coulter suggests is ideal but impossible to follow out in the average hospital in the United States, unless such a hospital has a physiotherapy department. If we keep hammering away at various schemes for managing arthritic patients, there is no doubt that ultimately home physiotherapy can be used more effectively. One way home treatment might be brought to the patient is to organize a committee of doctors, nurses, and physiotherapists interested in arthritis, who could go out in teams, meet local physicians, and go over the situation. A visiting nurse or physiotherapist could be appointed to cover certain communities and to teach home treatment. It is only through a well-organized plan that we are going to be able to treat this large group of patients.

There should be an organized plan so that physiotherapists, family doctors, and people in the homes can receive an adequate amount of instruction in the care of joints. It is only through such an arrangement that we will be able to treat the majority of arthritic patients. What should be done is easy enough to suggest, but how to accomplish it is another matter.

The great tendency in treating arthritic patients is to give them heat, massage, or electricity. Too much of any of these is bad medicine. Members of the family can help the patient with his exercises after the acute inflammation has subsided. Exercises should always be active or active plus passive. Passive motion in an arthritic joint will increase inflammation in synovial membrane. Scar tissue and ankylosis may result. Heat is used at home to a large extent but I believe it is bad therapy, since heat will not cure arthritis. There is too much buying of bakers and diathermy machines by people who do not know how to use them or what the dose should be. I have seen patients who have had home baking to such an extent that their limbs looked as if they had been covered with blobs of chocolate.

DR. CHARLES L. LOWMAN, LOS ANGELES, CALIF.—Very often too great a jump is made from rest to exercise. When muscle atrophy exists, there should be a carefully graded progress from bed rest to active exercise of involved joints.

This can be best accomplished in water. The absence of weight load on the joints by the elimination of gravity makes possible a greater amount of muscular activity with its beneficial effect on nutritive, circulatory, and eliminatory processes, without the intraarticular pressure incident to work done out of water.

Greater range in the painless are even in a subacute joint can be gained in active movement of an assistive type when the advantage of the lift of buoyancy is used. For the advantage of general peripheral dilatation of vessels obtained by submersion in a warm bath can be supplemented by exercise, preferably, of course, in a therapeutic pool under technical guidance, but at home a limited amount of leg and arm work can be obtained by a fifteen to twenty minute period in a warm saline bath with less risk. Sea salt and commercial epsom salt can be used at very nominal expense.

Our practice in pool therapy is a sequential one. First, movements of the uninvolved areas of the body, especially abdominal wall muscles, are prescribed. These are important in order that a proper degree of resistance to the action of the diaphragm may be obtained, as the effect of any pump depends on the amount of compression as well as the force and range of the plunger stroke. Second, two sets of muscle groups are always activated for any movement of a part. Intrinsic muscles activate a given joint but their base of action must be concurrently fixed by extrinsic stabilizing groups. In arthritis both sets are atrophied from disuse or continued spasm. Consequently in subacute cases you can at least tone up the extrinsic muscles before the time when it is advisable to begin on the intrinsic ones. As these are chiefly trunk groups there is the added benefit of the improvement of spinal, abdominal, and respiratory function essential in combating the systemic part of the disease. Third, the joints involved may be exercised, never passively but actively or by active-passive movements. As the range or arc of motion even in an acutely painful joint is much greater in warm water, the reparative influence is more rapidly obtained and the mental fear complex which has been initiated previously is absent or rapidly subsides. Fourth, weight bearing can be graduated in water when the right kind of depth pools are available. The patient who has not been able to stand for a long time actually sees himself upright and his legs go through the greatest possible amount of steppage, with a weight load decreased to only a few pounds. The weight dosage is graded by gradually proceeding to shallower depths.

I agree with Dr. Coulter that with care on the part of the doctor and intelligent co-operation on the part of the patient and some member of the family, some home regime is not only possible but very desirable. We require patients to take enemas at home, to adjust the diets according to orders, to take sun treatments, to follow exercises after fractures, to douche their noses and gargle their throats for nose and throat affections, so why should we not expect them to carry out simple orders for physical therapy?

DR. PHILIP S. HENCH, ROCHESTER, MINN.—May I express complete approval of Dr. Coulter's views. Questioning a large number of arthritic patients, I found that 75 per cent had consulted osteopaths or chiropractors. The reasons they gave for such defections from orthodox practice were that their physicians either gave them no physiotherapy or gave it to them haphazardly, "not often enough to keep me relieved," or because physiotherapy in the physician's or professional physiotherapist's office was too expensive, and more costly than they could get it elsewhere. We cannot expect much from physiotherapy applied only twice a week, or even daily for only twenty-one days, the usual "course." It is ridiculous to expect best results from physiotherapy used yesterday but not today or tomorrow. It is as if we wore a raincoat yesterday when it was raining hard but not today when it is pouring and wonder why we are still wet.

Few patients, however, can long afford professional physiotherapy more than two or three times a week. They should be permitted, indeed urged, to supplement such service with home treatment. In this country and in Europe, there are very few spa physicians who make a real effort to teach the departing patient home physiotherapy in order to project into the patient's home environment at least some of the benefits of the spa. For some years it has been our custom at the Mayo Clinic to give every arthritic patient and where possible his relatives also, as a supplement to other measures, detailed instructions in simple and harmless methods available for home use. A physiotherapy highbrow may scorn such procedures as inadequate, but they are a lot better than nothing, and fill the need felt by the patient who has sought relief from a hot bath, a strip of flannel and a hot iron, a farm oven or a bag of heated sand, salt or oats. If his physician does not tell him of better methods, he will continue his amateur efforts or get help from the cultist.

Now for home-physiotherapy we have the approval of Dr. Coulter, chairman of the Council on Physical Therapy of the American Medical Association. Although home treatment entails a little danger at the hands of physicians and patients inadequately instructed in its principles and details, surely safe methods can be taught by intelligent physicians and technicians to intelligent patients.

DR. RICHARD KOVACS, NEW YORK, N. Y.—May I call attention to the menace of advertising diathermy machines for home treatment over the radio and by mail. This is evidently a profitable venture for at present no less than four firms are advertising in New York with special emphasis on good results in arthritis. This situation is due to the laxity of control over radio advertising and unfortunately also to the attitude of some physicians in condoning this dangerous practice. We are combating it by spreading intelligent information through the Bureau of Information of the New York Academy of Medicine and the Better Business Bureau. We are confident that this fad will ultimately run its course just as that of home treatment by ultraviolet rays did, but in the meantime it is a real menace and might spread to other localities.

DR. COULTER (closing).—I think the family physician will have to be the one to treat chronic arthritis if Dr. Ober figures there are 70,000 arthritic patients in Massachusetts receiving no treatment whatever. The family physician is competent to treat arthritis and to use the simple methods of home treatment. He and the medical student should be instructed in the use of the simple physical agents, such as heat, massage, and exercise. The family physician must direct home physical therapy and can do it very easily with the simple directions we give. The best place to give it is in the home, since it will reduce the cost of medical care which we hear so much about today.

CHRONIC ATROPHIC ARTHRITIS: THE EFFECT OF A HIGH CARBOHYDRATE DIET AND INSULIN ON THE SYMPTOMS AND RESPIRATORY METABOLISM*

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THIS study was made primarily to observe the effect of overnutrition on patients with chronic atrophic arthritis who had lost weight excessively. Since there is some controversy concerning the proper carbohydrate content of the diet for patients with chronic atrophic arthritis, and since, in view of this discussion, it seemed desirable to observe the effect of a high carbohydrate diet on such patients for long periods, such a course was selected as the method of obtaining overnutrition. As our observations continued, no contraindications for the employment of such a diet became evident.

Such a study appeared, also, to afford an opportunity to observe the effect of hypernutrition and a high carbohydrate diet during the process of increasing body weight on the respiratory metabolism both with and without insulin.

Method of Study.—Upon admission the patients were given a high carbohydrate diet (425 to 500 gm. daily) with adequate protein to keep them in nitrogen equilibrium and sufficient fat to bring their total caloric intake from 2,200 to 2,700 calories daily. As far as possible the patients were allowed to choose their own articles of food. The diets were calculated by the same method as is used in estimating weighed diabetic diets, which we thought was sufficiently accurate for the purpose of this study. Food which was not eaten was returned to the diet kitchen and when this was carbohydrate, an equivalent amount of carbohydrate was sent back to the patient in the form of orange juice. When the patients were receiving insulin, orange juice was usually given between meals and also in the evening, excepting when the patient was to go to the metabolism laboratory the following morning. Then, if a hypoglycemic reaction occurred, only 50 c.c. of orange juice was given. Usually the patient's respiratory metabolism was determined at weekly intervals. This occasionally was not possible because the patient could not be made sufficiently comfortable for a successful test. The expired air was collected in the gasometer for three periods of fifteen minutes each. The air from the first period was discarded and gas analyses made on the others in the Haldane apparatus. It was required that the ventilation volume and the CO₂ percentages of the expired air check rather closely before the test was accepted, so that the effect of hyperventilation could be eliminated as far as possible.

The patients who were able were encouraged to be as active about the wards as they wished; some of them were permitted to leave the hospital for auto rides and to sit in the open air when the weather was favorable.

*From the Buffalo General Hospital and School of Medicine, University of Buffalo.

Most of the patients received some form of physiotherapy—ultraviolet light, infra-red light treatments, and gentle massage. If they had pain, acetylsalicylic acid was given. A few of them required sedatives at night. Most of them received *Streptococcus hemolyticus* (AB₁₃) vaccine in small doses for varying periods of time.

AVERAGE DIET

Carbohydrate 500 gm. Protein 60 gm. Fat 50 gm. Calories 2,690

<i>Breakfast:</i>		GRAMS
Choice of	Cooked cereal (dry weight)	30
One	or	
	Cornflakes, shredded wheat	30
	Bread (rye, white, or whole wheat)	60
	Sugar	20
	Skimmed milk	120
	10% fruit juice	200
	10% fruit	160
	Jam or jelly	60
	Butter	10
	Coffee or tea	

<i>Noon Meal:</i>		
Choice of	Lean meat	30
One	or	
	Fish (plus 6 gm. butter)	40
	5% vegetable	120
	Baked or boiled potato or rice	90
	Bread (rye, white, or whole wheat)	60
	Buttermilk or skimmed milk	60
	Sugar	26
	Butter	19
	10% fruit juice	200
	Canned fruit	100
	Jam or jelly	30
	Coffee or tea	

<i>Evening Meal:</i>		
Choice of	Egg (one)	
One	or	
	Cottage cheese (plus 8 gm. butter)	30
	5% vegetable	120
	10% vegetable	120
	Potato (baked or boiled)	120
	10% fruit juice	200
	Canned fruit	100
	Bread (rye, white, or whole wheat)	60
	Butter	15
	Sugar	33
	Buttermilk or skimmed milk	120
	Coffee or tea	

CASE REPORTS

CASE 1.—History: M.M., a telephone operator aged fifty-two, admitted to hospital Jan. 11, 1934, and discharged Nov. 14, 1934. She had been well until the onset of arthritis in 1929 which began with pain and stiffness in various joints. Deformity of the wrists and hands had appeared in the past two years. She had not been able to work for about a year. Her loss of weight had been gradual for the past five years from 140 to 106 pounds.

Examination: An undernourished woman confined to bed because of weakness and pain. Double dentures. Throat red; tonsils imbedded. Joints: right shoulder, rotation limited and painful. Right elbow, motion painful. Wrists, extensive swelling and limitation of motion. Hands, the phalangeal joints were swollen, deformed and tender to pressure. The patient was not able to make a fist. The hands showed ulnar deviation and atrophy of the lumbricales muscles.

Laboratory Examinations: Urinalyses, all negative. Blood: red blood cells 4,360,000 per c. mm.; hemoglobin, 70 per cent (Sahli). Sugar (fasting) 126 mg. per 100 c.c. Sedimentation rate, 30 mm. one hour, corrected for cell volume. Agglutination of hemolytic streptococcus (AB_{13}), positive to a dilution of 1280 of blood serum.

Course: Upon admission a diet of 450 gm. of carbohydrate, 60 gm. of protein, and 50 gm. of fat was prescribed. This she ate fairly well, but frequently it was necessary to make up some of the carbohydrate in orange juice, and consequently the protein and fat were a trifle less than that allowed. Soon after she entered, a mild respiratory infection developed which persisted for nearly a month; this was accompanied by several short bouts of fever. During this period her weight increased slightly.

Acetylsalicylic acid or amidopyrine was given as necessary for pain and phenobarbital was often required at night. Gradually it became apparent that there was more motion in the involved joints and that she was requiring less medication for pain.

Beginning March 12, 1934, 12 units of insulin were given before each meal. At this stage she had gained six pounds. The dosage of insulin was rapidly increased to 18 units, a point where mild hypoglycemic reactions occasionally occurred. Insulin was continued until Sept. 7, 1934, when salt solution was substituted. At this time her weight was 145.5 pounds. She had changed from a bedridden patient to one who was able to be up all day, go for short walks, take a tub bath and care for herself generally. Her attitude toward her illness had likewise improved; on admission she was disgruntled and unhappy; now jovial and optimistic concerning the future. She had required no medication for the relief of pain since April and none for sleep since July. She was discharged in November in excellent condition. Her weight was 149 pounds. She was requested to follow her hospital diet as closely as possible at home. Unfortunately, she was thrown into an unavoidable domestic situation which compelled her to do more work than she could comfortably tolerate. Nevertheless, during the past seven months she has carried on with but moderate discomfort. Pain has been present particularly in the hands. Her appetite has been somewhat reduced and at the present time (May 1, 1935), her weight is 137 pounds.

CASE 2.—*History:* B. L., a widow aged 66, admitted April 18, 1933, and discharged July 18, 1934. She had extensive atrophic arthritis which had started two years previously in the middle finger of the right hand. In the past year it had involved the toes, knees, hips, other fingers, and the left elbow and shoulder. She had had considerable pain and had been essentially bedridden for several months prior to admission. Her appetite had been poor, during which time she had lost 40 pounds.

During the winter prior to the inception of the arthritis she had had frequent sore throats, but it could not be specifically determined that a throat infection had occurred just before the first joint had been involved. Her teeth had been extracted several years previously. In July, 1932, she had Bell's palsy which ran a course of several weeks. At that time, previous to the development of the arthritis, the laryngologist had reported a nasopharyngitis with questionable sinusitis.

Examination: A considerably emaciated woman who did not appear to be quite the reported age. She is badly crippled with typical atrophic arthritis as stated in the present illness. Her legs are contracted.

Laboratory Examinations: Urinalyses, negative. Blood: red blood cells 4,500,000; white blood cells 8,800 per c. mm.; polymorphonuclears 52 per cent; hemoglobin 70 per cent (Sahli). Blood Wassermann reaction, negative. Sugar (fasting) 124 and 114 mg.; urea nitrogen 15 mg.; uric acid 2.8 mg. per 100 c.c. Agglutination, *Streptococcus hemolyticus* (AB_{13}), positive to a dilution of 2560 of blood serum. Sedimentation rate, 66 mm. at the end of one hour.

Course: On admission her weight was 97 pounds. During the first fifteen days of her stay, she ingested daily about 360 gm. of carbohydrate, 45 gm. of protein and 61 gm. of fat. This totaled 2,190 calories, which was considerably less than that prescribed. During this period her weight increased to 104 pounds. In the next period, sixteen days, she received insulin, 16 units a.c., and ingested an average of 395 gm. of carbohydrate, 43 gm. of protein, and 57 gm. of fat. During this period she developed a typical attack of acute follicular tonsillitis which apparently did not produce any change in her joints. This did

not cause any weight loss. In the third period, twenty-one days, 20 units of insulin were given before each meal. The average daily diet was carbohydrate 437 gm., protein 44 gm., and fat 60 gm., totalling 2,464 calories. At the end of the third period her weight was 108 pounds. In the fourth period, thirty-nine days, the diet was similar, about 2,500 calories. Insulin, 24 units before meals, was given. Her weight increased to 116 pounds. In the fifth

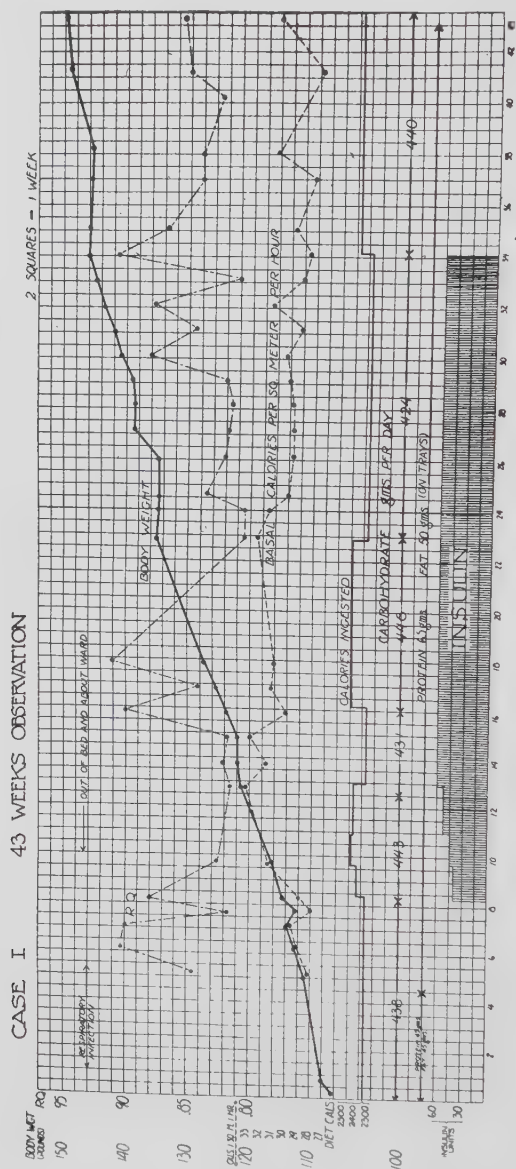


Chart 1.

period, nineteen days, only sterile salt solution was injected before meals. Her average daily food consumption was 2,530 calories. Her weight increased to 120 pounds. During her study thus far, there had been slight but definite improvement in her general well-being. She had less pain and could handle herself in bed very much better. On Aug. 14, 1933, her tonsils were removed under a general anesthesia. She was not able to resume her regular diet until August 26, and had lost six pounds. Since her appetite was unimpaired, insulin was

not resumed. By September 18, she weighed more than she did preoperatively. A diet of 460 gm. of carbohydrate, 50 gm. of protein, and 60 gm. of fat was continued up to her discharge on July 18, 1934. Her weight on July 7 was 145 pounds. The pain had gradually reduced and the range of motion had generally increased so that by September, 1933, she was able to get into a chair. She could have walked but for the contractures at the knees.

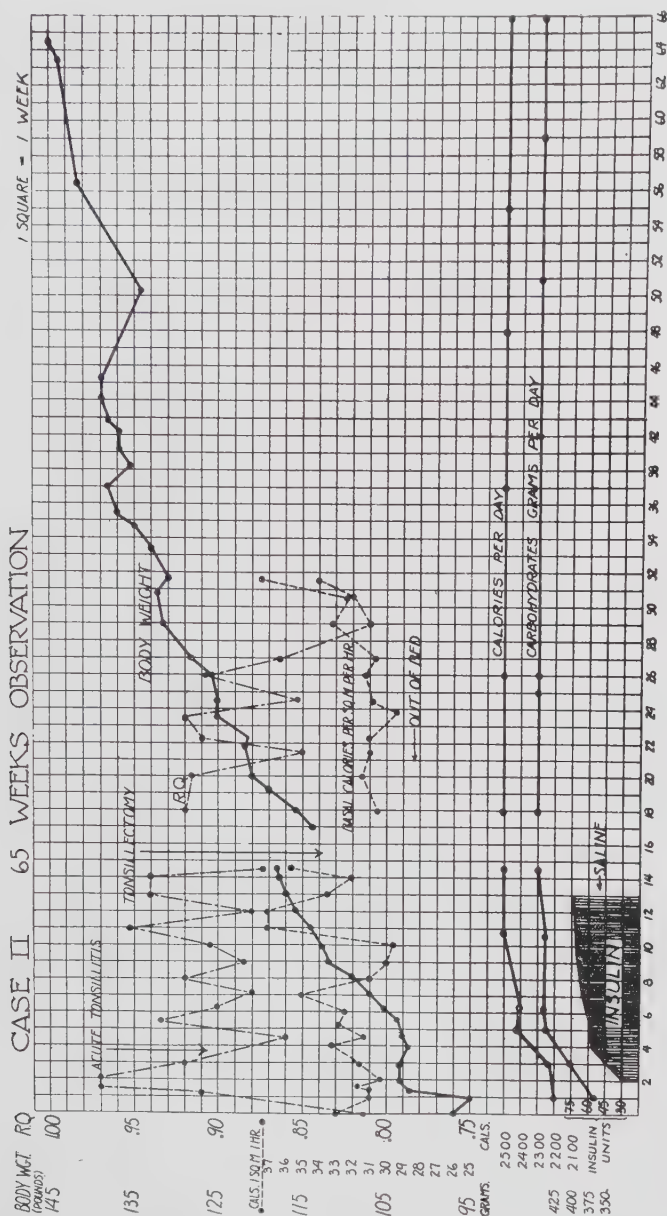


Chart 2.

She required no medication for pain but occasionally received barbitol at night. A survey of her state on Feb. 17, 1934, was as follows: "Her back is still painful while lying flat; her left hand and wrist are much improved—no redness or pain on pressure and the range of motion is definitely increased. The left elbow and shoulder are not involved, whereas on admission she had about 30 per cent range of motion in these two joints. Right hand and

wrist, less swelling and pain on motion. Right elbow and shoulder, no pain; motion is excellent in all directions. She can reach to her back which was not possible upon admission. Hips, motion is painful while lying on her back, but not so when lying on her side. Knees, there is essentially no change in motion, but they are less painful. Ankles, no swelling—sometimes are painful. She is now able to get around the wards and corridors in a wheel chair." From this time until her discharge in July, 1934, there was less noticeable improvement, and it appeared that the maximum benefit had been attained. She returned to her home until readmission in January, 1935, for the purpose of considering the advisability of operative measures to her knees. Then it was learned that there had been a gradual return of pain and swelling in the right wrist and ankles, particularly the former. While at home her appetite had diminished and she lost ten pounds. She was obviously discouraged. The high carbohydrate diet was again instituted but she took only a portion of it. After two weeks' observation without there being any change in her state, insulin, 20 units a.c., was again given. In a few days she developed pain which did not subside with the substitution of beef for pig insulin but did so a few days after the withdrawal of insulin altogether. At the present time (May 1, 1935) when she is allowed to eat what she chooses, her daily food consumption is only 1,600 calories.

CASE 3.—History: M. N., housewife aged fifty-two, had been in the hospital since Oct. 6, 1934. She had been well up to a year and a half prior to her entrance when "neuritic" pains began in the knees and shoulders. The knees became swollen and tender in November, 1933; involvement of the wrists began in April, 1934. Gradually, the pain, swelling, limitation of motion and deformity increased in the knees and wrists. The ankles and shoulders were affected, but to a lesser degree.

Her maximum weight was 155 pounds eight years ago. At the onset of the arthritis it was 135 pounds. Now it is 104 pounds. She believes that worry over the arthritis rather than loss of appetite accounts for the loss of weight.

Her teeth had all been removed eight years ago. She had had no significant infection recently. A carbuncle which had required excision had occurred on the right arm four years ago.

Examination: A somewhat pale, undernourished woman who had atrophic arthritis. The tonsils were the buried type; material could be expressed from them. The joints were as indicated in the history. Otherwise, the physical examination was not remarkable.

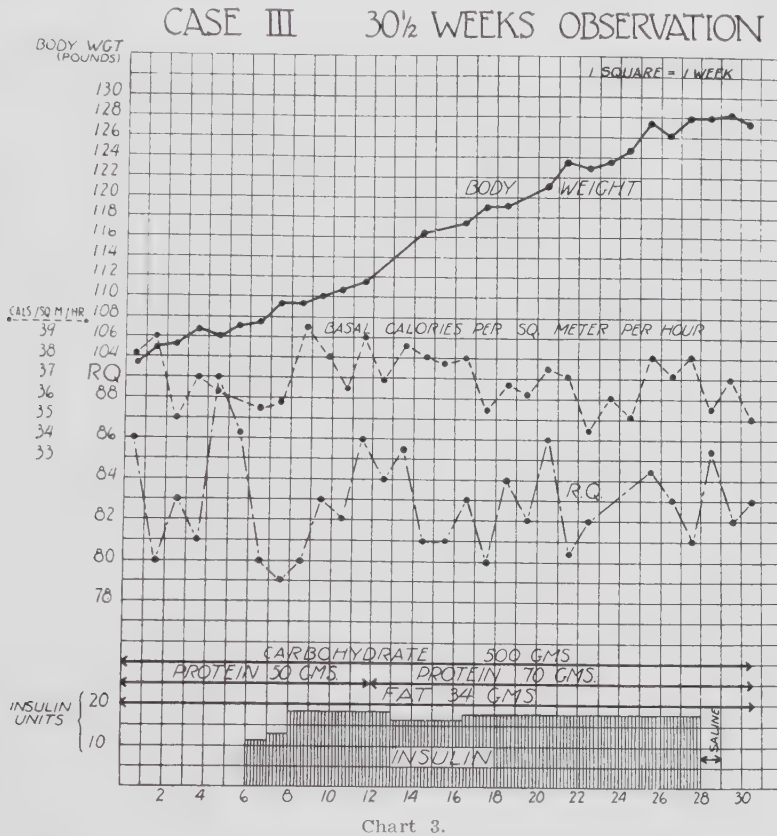
Laboratory Examinations: Urinalyses, negative. Blood: red blood cells, 4,100,000; white blood cells 7,600 per c. mm.; polymorphonuclears 67 per cent; hemoglobin 70 per cent (Sahli). Blood Wassermann reaction, negative. Sugar (fasting) 121 mg.; urea nitrogen, 11 mg. per 100 c.c. Sedimentation rate on admission, 39 mm. in one hour; on Jan. 18, 1935, 34 mm. in one hour, both corrected for cell volume. Agglutination with *Streptococcus hemolyticus* (AB₁₃), positive up to 1-1280 dilution of serum.

Course: Upon admission she was given a diet of 500 gm. carbohydrate, 50 gm. of protein, and 34 gm. of fat. She ingested, with great regularity, all the carbohydrate and nearly all the fat, but fell short of the protein allowance about 5 gm. daily during the period of six weeks before insulin was given. While she was ingesting 2,500 calories daily her weight increased 3.5 pounds. Insulin was then started, 12 units a.c., and gradually increased to 18 units. She had but an occasional hypoglycemic reaction. The diet remained the same for another six weeks during which time her weight increased another 3.5 pounds. Then for a period of five weeks the protein in her diet was increased to 70 gm. During this period her weight increased 6.5 pounds. The fat in the diet was now increased to 50 gm. daily. During this period, nearly twelve weeks, the patient gained 10 pounds. The fasting blood sugar just before insulin was stopped was 113 mg. per 100 c.c. The blood sugar taken just before the noon insulin dosage was 92 mg. at one time and 106 mg. at another. Three days after the withdrawal of insulin the fasting blood sugar was 121 mg. per 100 c.c. and nine days after, the digestion blood sugar was 138 mg. The urine was examined for sugar four times daily for a week following the withdrawal of insulin. No glycosuria was found even though the patient continued to ingest a high carbohydrate diet. During the entire study the patient received her full quota of carbohydrate, since the carbohydrate portion of her diet which was returned to the diet kitchen was brought back

to her in the form of orange juice. The protein and fat contents of her diet were usually somewhat less than the prescribed amount. However, the average daily consumption of food was always in excess of 2,500 calories.

Since Oct. 22, 1934, she has received small doses of streptococcus vaccine (AB₁₃), subcutaneously. At the present time she receives three million organisms every ten days. Also, she is being treated with ultraviolet and infra-red light along with gentle massage of her joints.

After she had been under observation for a month, it was noted that she had less pain and that her joints had more freedom of motion. After two months she was able to walk to the bathroom with the aid of a cane, and with very little pain. She can now fully



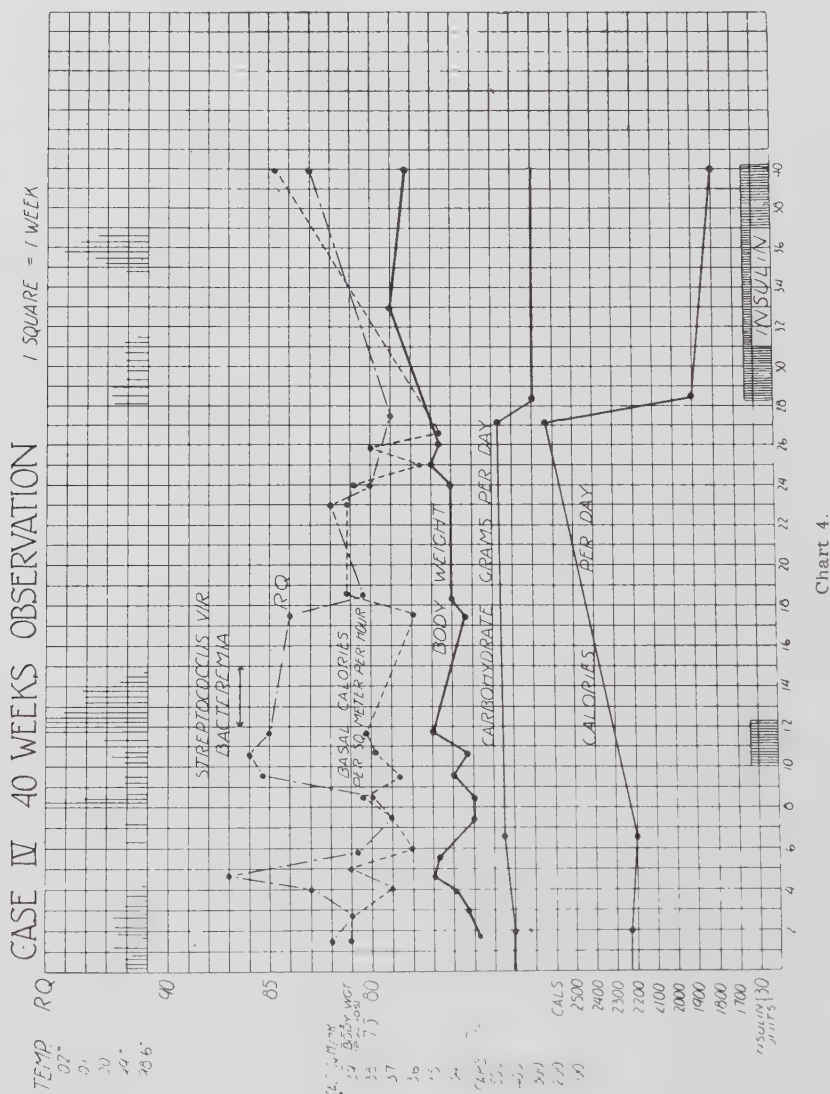
extend the left leg and can almost completely extend the right one without pain. This represents an increase of thirty degrees in the range of extension. Also, she can lift both legs from the bed in an extended position which formerly she could not do. Now, most of the pain and stiffness is in the right knee and right wrist.

CASE 4.—History: J. G., a schoolgirl, aged eighteen, admitted Feb. 22, 1934, has been a patient in the hospital since that time. In April, 1932, a month after an attack of scarlet fever, she developed pain, swelling, and redness in the fingers and ankles. This process gradually spread to the other joints of the body including the back, hips, and jaws. Tonsillectomy was done in May, 1932, but it had no beneficial effect. Her loss of weight had been 40 pounds.

Examination: An emaciated young girl whose joints showed the typical changes of advanced atrophic arthritis of the fourth stage. There was a systolic murmur at the mitral

region of the precordium which was not widely transmitted. A few scattered râles were heard at the right supraclavicular region.

Laboratory Examinations: Urinalyses, negative. Blood: red blood cells 4,460,000; white blood cells 8,200 per c. mm.; polymorphonuclears 60 per cent; hemoglobin 65 per cent (Tallqvist). Wassermann reaction, negative. Sugar (fasting) 95 mg. on admission, 90 mg. in January, 1935; urea nitrogen 10 mg. per 100 c.c. Sedimentation rate,* 33 mm., on admission in August, 1934, 60 mm., and in January, 1935, 25 mm. at the end of one hour, all corrected



for cell volume. Agglutination, *Streptococcus hemolyticus* (AB₁₃), positive up to a dilution of 1:1280 of serum. Six blood cultures, taken during febrile periods, were all negative except one which was taken during a chill. This showed one definite colony of *Streptococcus viridans*. Agglutinations of blood serum were negative for *B. typhosus*, *B. paratyphosus* A and B, and *B. abortus*.

*All sedimentation rates were done by the Wintrobe method.

Course: Her case seemed like a hopeless one from the first, but since no provision could be made for her at home or in another hospital, it seemed necessary for us to keep her under observation. She usually had some afternoon fever and on two occasions, once in April and once in May, she had a sharp rise of temperature following a chill which immediately subsided. Later on, longer bouts of fever occurred.

Upon admission she was given a diet of 450 gm. of carbohydrate, 60 gm. of protein, and 62 gm. of fat. Her appetite was poor and great difficulty was experienced by the attendants in encouraging her to eat. She usually received the full carbohydrate quota of her diet but she appeared to have considerable aversion to protein and fat. Her weight upon admission was 70 pounds. Her best weight was reached on August 15, 1934, when she weighed 74 pounds. Her diet consisted principally of carbohydrate although there were days when she took her full diet. Insulin, 12 units a.c., which was started on Sept. 24, 1934, at the time when her appetite was beginning to wane, had no effect. On Nov. 20, 1934, her weight was 73 pounds.

The signs at the right pulmonary apex were watched rather carefully. It became evident that there was increasing activity. An x-ray taken in May, 1934, showed both pulmonary apices to be slightly hazy. By December, 1934, there was distinct cloudiness on the right side. By May, 1935, the right upper pulmonary lobe showed marked density and mottling. Physical signs at that time indicated a rather extensive involvement with probable cavity formation. Her fever which has been present from time to time is now quite regularly present, running up to 101° to 102° F. in the afternoon.

Comments: Because of the positive blood culture on one occasion and the mitral systolic murmur over the heart, the diagnosis of malignant endocarditis had been considered. With the signs, however, at the right pulmonary apex, it seems probable that she has pulmonary tuberculosis. She failed to gain weight in spite of a rather adequate caloric intake over a long period.

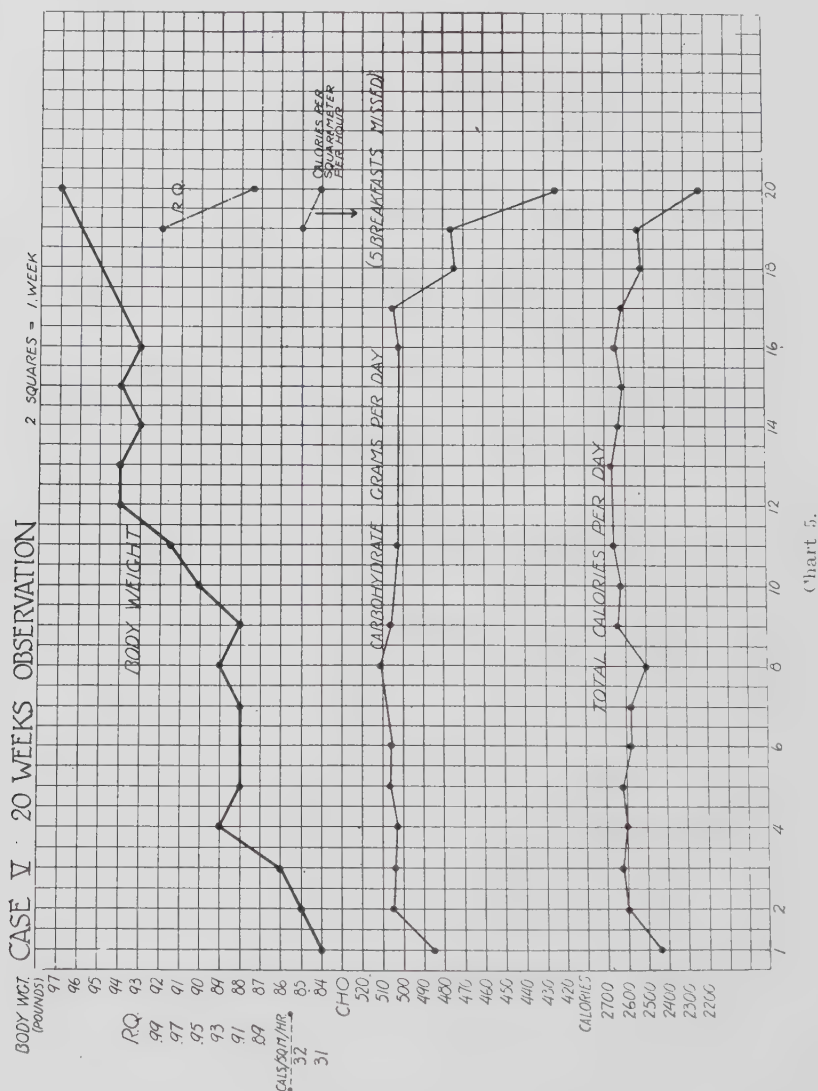
CASE 5.—History: J. A., housewife aged forty-four, admitted to the hospital May 2, 1934, and discharged Oct. 2, 1934. The arthritis had begun in 1922 involving only the left hip. It had progressed rather slowly. Now both knees, hips, wrists, elbows, and shoulders are affected. The right hip which had been involved for seven years gives her the most distress. During the past ten years she had lost 40 pounds. This she attributed to a poor appetite. The only treatment had been the removal of a few teeth, and occasionally artificial heat had been used.

Examination: An undernourished woman (weight 84 pounds), who was considerably crippled with atrophic arthritis. Four teeth remained; the gums were infected. The involved joints were swollen, and their motion was reduced. The movement of the shoulder and left hip was particularly limited.

Laboratory Examinations: Urinalyses, negative. Blood: red blood cells 4,800,000; white blood cells 8,100 per c. mm.; polymorphonuclears 67 per cent; hemoglobin 71 per cent (Newcomer). Blood Wassermann reaction, negative. Sugar (fasting) 132 mg.; urea nitrogen 11 mg. per 100 c.c. Gastric contents showed achlorhydria even after the injection of histamine. Sedimentation rate, 34 mm. on admission and 55 mm. in August, at the end of one hour, corrected for cell volume. Fluid aspirated from the right knee joint on May 10 showed 2,000 cells per c. mm.; specific gravity 1.026; Rivalta test, positive. Smear of sediment showed the cells to be mostly polymorphonuclears, but no bacteria either on direct smear or culture were found. Respiratory quotients, after the high carbohydrate diet, 0.89 (average of six determinations); basal calories per square meter per hour, 31 (average of several determinations).

Course: Upon admission a diet of 500 gm. of carbohydrate, 60 gm. of protein, and 50 gm. of fat was prescribed. She ingested her full allowance of carbohydrate but did not take all of the protein and fat. Nevertheless, her daily food consumption was always in excess of 2,600 calories. Gentle massage and ultraviolet light therapy were given three times a week. The patient took her diet so well that insulin was not used. Her increase in body weight was steady, 13 pounds in twenty weeks. There likewise appeared to be a steady reduction of joint pain and swelling. Upon discharge there was distinct improvement in the range of motion of most of the involved joints.

CASE 6.—*History*: N. B., a woman aged twenty-one years, admitted to the hospital Nov. 2, 1934, and discharged April 19, 1935. She dated her illness to October, 1932, when she noticed a loss of appetite and weight with increasing fatigue after work as a clerk. In March, 1933, pain and reduced motion were observed in the right shoulder. This process spread rather rapidly to the other joints of the upper extremities in spite of a tonsillectomy which was done in May, 1933. Later, following an attack of pharyngitis, the knees became



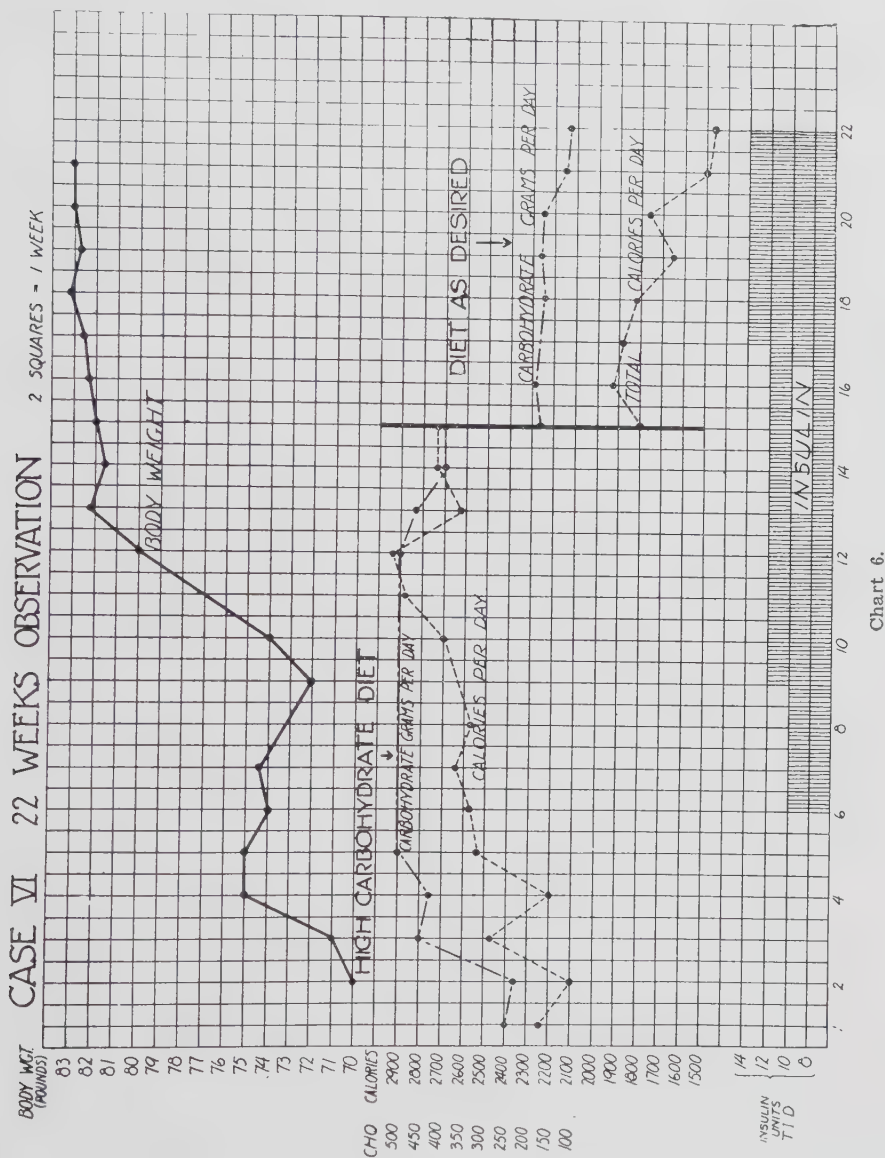
involved. These were placed in casts for three months. The ankles were the last joints to be affected. The total weight loss since the inception of her illness was 30 pounds.

Examination: An undernourished young woman who was confined to her bed because of a crippling atrophic arthritis. There was generalized moderate lymphadenopathy. There was obvious infection about one tooth (this was later removed).

Laboratory Examinations: Urinalyses, negative. Blood: red blood cells 4,050,000; white blood cells 10,300 per c. mm.; polymorphonuclears 68 per cent; hemoglobin 86 per cent (Sahli). Wassermann reaction, negative. Sugar (fasting) 104 mg.; urea nitrogen 12

mg. per 100 c.c. Sugar taken during digestion while receiving a high carbohydrate diet and 10 units of insulin a.c. was 134 mg. per 100 c.c. Sedimentation rate, 39 mm. at the end of one hour, corrected for cell volume. Agglutination of *Streptococcus hemolyticus* (AB₁₃), positive up to a dilution of 1-2560 of serum. Basal metabolic rate, minus 0.2 per cent.

Course: As is indicated in Chart 6, the patient received a moderate fat and carbohydrate diet for the first two weeks. Then the diet was changed to 500 gm. of carbohydrate, 50



gm. of protein, and 50 gm. of fat. She also received ultraviolet light treatments and gentle massage three times a week. Ferric ammonium citrate, 2 gm., was given thrice daily. Cod liver oil, 8 c.c., daily. *Streptococcus vaccine* (AB₁₃) was given weekly up to doses of 1 c.c. subcutaneously.

After she had been receiving the high carbohydrate diet for four weeks her weight had increased 5 pounds. Then insulin was started, 10 units before meals and gradually increased to 14 units. She did not gain satisfactorily even though her diet seemed adequate,

At the end of the tenth week the protein and fat content of her diet was increased. By the end of the fourteenth week her weight had increased 11.5 pounds. It had been difficult all along to get this patient to eat. Finally she rebelled. As a compromise we offered to let her make out her own menus and have what she wished. This she did for the next six weeks. The result as indicated on Chart 6 demonstrates the difficulties one encounters in getting such patients to voluntarily eat an adequate diet in spite of, in this case, the supposed appetizing effect of insulin. Her weight increased but 1.5 pounds during this period.

She did not improve as some of our other patients, but had on the whole less pain and swelling of the joints. For a time she seemed encouraged and in better spirits. During the

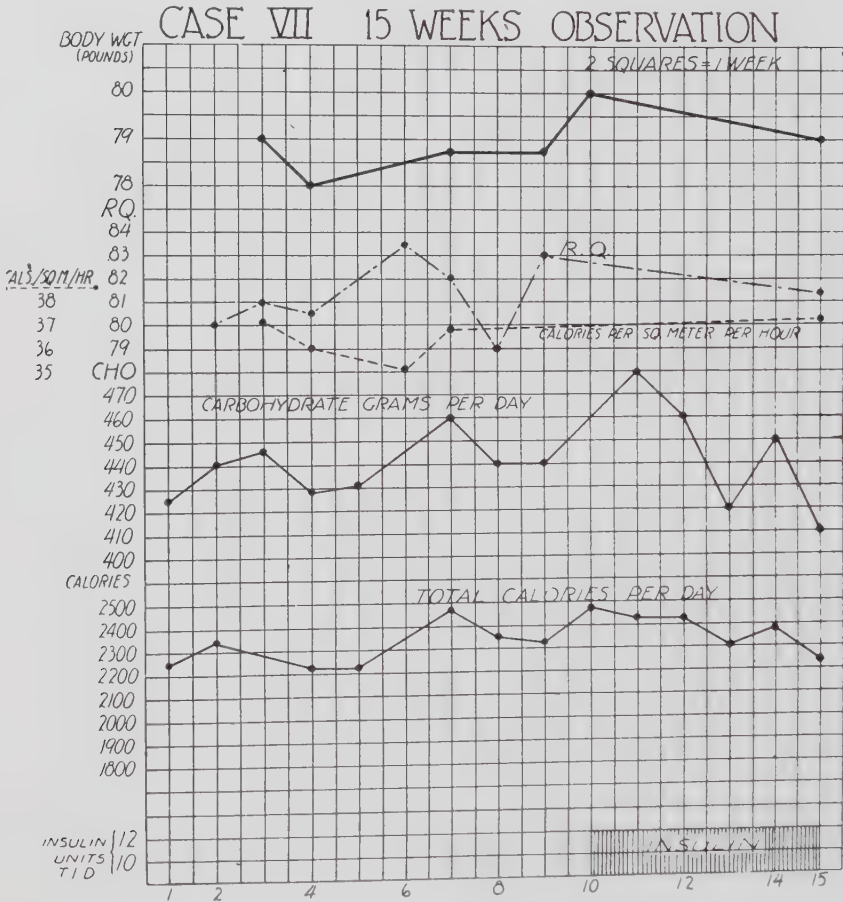


Chart 7.

last two months of her hospital stay she was up occasionally on crutches but never walked any distance. There were days at a time when it was impossible to get her out of bed.

CASE 7.—History: M. B., housewife aged thirty-nine, was admitted to hospital on March 2, 1934, and was discharged June 15, 1934. She had a most extensive and advanced atrophic arthritis which involved all the joints of the body including the back. The illness had begun in 1924 following an appendectomy. It had gradually become universal. She had not walked even with the aid of crutches since December, 1933. She had been in many hospitals and had had various types of treatment. Her weight prior to the onset of the disease was 120 pounds; on entrance she weighed 79 pounds.

Examination: A completely crippled, emaciated woman who had extreme deformity of all the joints of the extremities except the fingers and toes. Mouth could be opened about one inch. The patient had to be fed. The legs were contracted on the thighs.

Laboratory Examinations: Urinalyses, negative. Blood: red blood cells 4,500,000; white blood cells 6,200 per c. mm.; polymorphonuclears 75 per cent; hemoglobin 80 per cent (Tallqvist). Wassermann reaction, negative. Sugar (fasting) 107 mg.; urea nitrogen 11 mg. per 100 c.c. Sedimentation rate, 79 mm. at the end of one hour, corrected for cell volume.

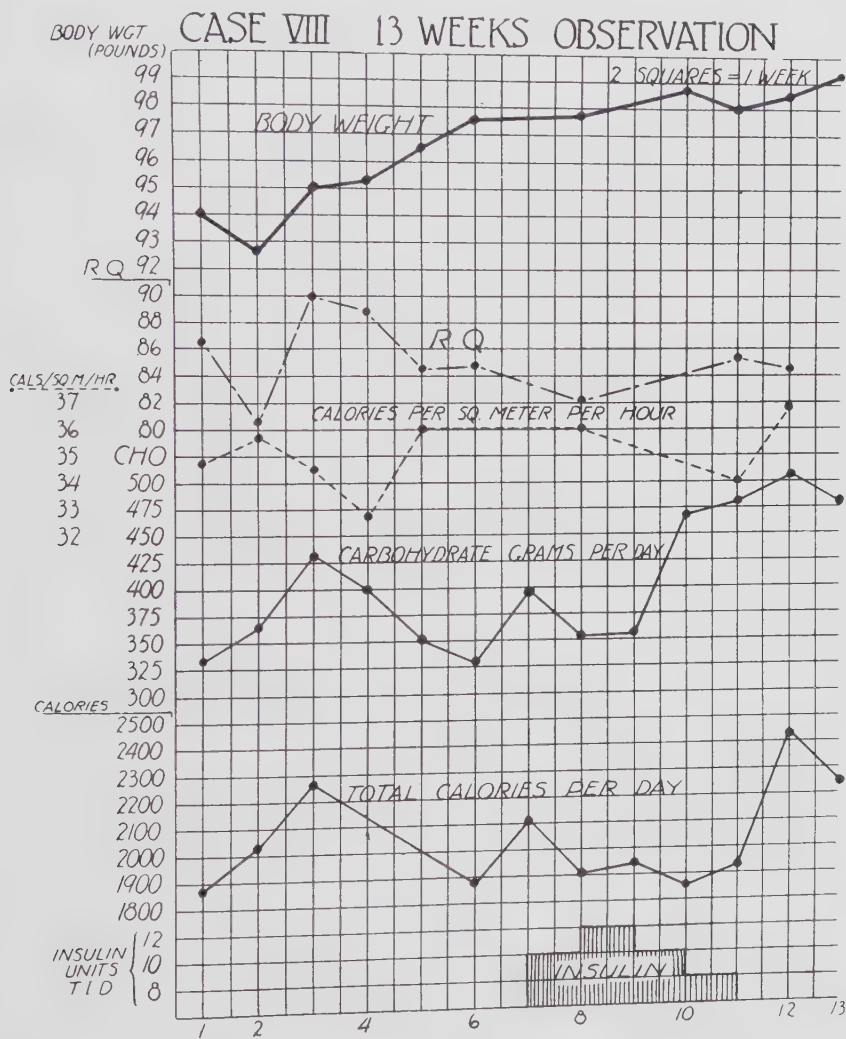


Chart 8.

Agglutination of *Streptococcus hemolyticus*, positive up to a dilution of 1:2080 of serum. Gastric contents showed the presence of free hydrochloric acid. Respiratory quotient while taking a high carbohydrate diet varied between 0.80 and 0.86. Basal calories per square meter per hour varied between 34.7 and 37.7 (six determinations).

Course: On admission she was given a diet of 450 gm. of carbohydrate, 60 gm. of protein, and 60 gm. of fat. Considering her badly nourished state, she ate remarkably well, as indicated in Chart 7. Her daily consumption of food ranged between 2,250 and 2,470 calories. She usually took most of the carbohydrate allowed. At the tenth week, her

weight having remained at 79 pounds, insulin was started, 12 units before meals. This was continued for five weeks without there having been any increase in food ingested or increase in weight.

She had slight fever, 100° F., occasionally. This was unexplained. On the whole, as would be expected, there was no essential change in her state, although she did have less pain and the joints of the upper extremities did appear to have some increased range of motion.

CASE 8.—History: D. W., a woman aged fifty-four, was admitted to the hospital on Aug. 25, 1933, and was discharged Jan. 3, 1934. She had had severe attacks of joint pains since May, 1932. There had been recurrent swelling and redness of the involved joints but these never subsided entirely. The fingers of both hands, left wrist, right shoulder, and right elbow were principally involved. The knees and ankles were affected but not so extensively. It appeared from her "past illness" that she had had fleeting, mild joint pains following a respiratory infection in 1928. Also, in the same year urinary symptoms, frequency, urgency, and burning, had been present. She had lost 25 pounds in the past year. Twenty-three years ago she had probably had an osteomyelitis of the coccyx which was opened twice. Her teeth had all been removed two years previously because of pyorrhea.

Examination: The patient was an undernourished woman with atrophic arthritis involving the joints as stated in the history. The knees and shoulders were normal objectively but gave pain on motion. The ankles were swollen and painful on pressure. There were a few rales in the right subscapular region with bronchovesicular breathing. There was a tender mass in the upper right quadrant, probably kidney.

Laboratory Examinations: Urinalyses all showed a trace of albumin, no sugar, and the sediment always showed many leucocytes. Blood: red blood cells 4,600,000; white blood cells 5,600 per c. mm.; 71 per cent polymorphonuclears; hemoglobin 75 per cent (Sahli). Wassermann blood reaction, negative. Sugar (fasting) 105 mg.; urea nitrogen 11 mg.; calcium 9.5 mg.; phosphorus 3.5 mg.; uric acid 2.5 mg. per 100 c.c. Respiratory quotient, varied from 0.81 to 0.89 (six determinations). Basal calories per square meter per hour, varied from 32.7 to 37.1.

Course: On Sept. 2, 1933, she was given a high carbohydrate diet as indicated on Chart 8. She did not eat well, usually less than 2,000 calories. She had, however, a urinary tract infection and frequently had slight fever. The bladder urine showed a few leucocytes with many small gram-negative bacilli. The injection of sterile water into the right renal pelvis reproduced the pain which the patient had experienced in the upper right quadrant. The ureteral urine, however, was clear. It was thought unwise to do a retrograde pyelogram. X-ray of the kidneys after the intravenous injection of skiodan showed the right kidney pelvis to be definitely larger.

Her weight remained between 93 and 95 pounds for the first six weeks. Then she was given insulin, 10 units before meals. After this her average food intake was somewhat greater. At the end of the thirteenth week her weight was 100 pounds.

There was no essential change in her general state. At the time of her discharge she could use her hands very much better.

The Factor of Undernutrition in Chronic Atrophic Arthritis.—The majority of patients with this type of arthritis lose weight, especially when the joint lesions become multiple, and the loss of weight is usually commensurate with the severity of the arthritis. In our perusal of many textbooks and key articles on this subject, no accurate data on the loss of weight was found. Since it seemed important to know whether the patients that we had chosen for this study were representative of advanced arthritis in that stage, the weight loss of 18 similar patients in addition to those reported was determined. The maximum loss was 48 pounds, the minimum, 15 pounds, and the average, 28 pounds.

Others have attempted to increase the weights of individuals who had become poorly nourished during the course of arthritis. Howitt and Christie¹ en-

TABLE I
SUMMARY OF DATA

CASE	AGE (YEARS)	PERIOD OF OB- SERVATION (WEEKS)	WEIGHT LOSS BEFORE ADMISSION (POUNDS)	WEIGHT GAIN (POUNDS)	INSULIN PERIOD (WEEKS)	AVERAGE R. Q.	AVERAGE B.M.R. (PER CENT)	CLINICAL CHANGES
1	52	43	34	42	26	0.83	-12	From bedridden to ambulatory. Less pain.
2	66	65	40	50	11	0.90	- 3	Greater range of joint motion. Much less pain; greater range of joint motion. Could have walked if legs could be extended
3	52	31	31	24	25½	0.83	+ 7	Great improvement. Knees and hip joints much increased range of motion
4	18	33	50	4½	3	0.83	+ 1	No change in arthritis; pulmonary tuberculosis
5	44	20	40	13	0	0.94	-10	Considerably less pain and increased range of joint motion
6	21	22	30	13	16	----	----	Slight, but definite improvement
7	39	15	41	0	6	0.82	+ 2	No change in arthritis
8	54	13	25	7	4	0.85	+0.7	Slight improvement in joint symptoms

deavored to increase the weight of twenty patients with chronic atrophic arthritis. These were observed both in the hospital and as out-patients. They were given a diet which, in the opinion of these workers, exceeded the patients' requirements by 500 to 1,000 calories. Insulin in doses of 10 to 15 units twice daily was given for a period of six weeks. Some weight was gained in each case; the maximum was 10 pounds. The general health and well-being of all the patients was improved. Copeman² reported measurable improvement in three patients who had been given a pound of glucose daily in addition to a normal diet. During this period of observation, three to four weeks, the patients received increasing amounts of insulin up to 60 units daily. The weight gains were only 3 to 5 pounds. Eaton and Love³ treated 22 undernourished arthritic patients with a high caloric diet and insulin up to 90 units daily for short periods. The average weight increase was 12 pounds in four to seven weeks. With these gains the authors state that there was noticeable improvement in the arthritis. Dawson⁴ reported that he had given diets high in carbohydrate to a number of patients with rheumatoid arthritis and that rather marked improvement had followed.

SUMMARY AND CONCLUSIONS

Eight patients with advanced atrophic arthritis, all women, whose ages varied from eighteen to sixty-six years, were observed in the hospital, during which time they were fed a high carbohydrate diet. The shortest period of observation was fifteen weeks, while the longest was sixty-five weeks. All patients had lost weight excessively, the maximum being 50 pounds and the minimum, 25 pounds.

Seven of the patients received insulin for the purpose of observing its action on increasing appetite; also, the influence of the reduction of blood sugar on the arthritis. All patients were observed for varying periods on the diet alone before insulin was administered. During this fore-period every effort was made by all the hospital services to induce the patients to eat. Carbohydrate was given to them in many forms. After this preliminary study further nutrition was attempted by the use of insulin up to the point of the patient's tolerance. It will be observed by examination of the charts that the weight curve was not conspicuously steeper during the period of insulin administration. Nor was the amount of food ingested greatly increased. Following the sudden withdrawal of insulin, salt solution subcutaneously was substituted; usually this was not accompanied by any diminution of appetite.

Three patients, Cases 1, 2, and 3, those who had been under observation for the longest periods, made the greatest weight gains, 42, 50, and 24 pounds, respectively. They also made the greatest clinical improvement. The texture of the skin of the patients who gained weight also was noticeably changed from the thin, atrophic skin, which is so commonly seen in such patients, to one of a more normal elasticity and firmness. Two patients, Cases 4 and 7, even though they did ingest adequate calories, failed to gain; both had the maximum devastation of the disease. One patient, Case 5, who had gained a lesser amount, also improved remarkably.

Clinical improvement that was observed in these patients cannot be ascribed to a single measure because several factors were obviously operating—rest, free-

dom from worry, and exposure, and a large amount of vitamin C. As far as possible other adjuncts were employed in a minimum degree. The high carbohydrate diet did not produce any exacerbation of the arthritic process. Only one patient, Case 3, developed arthritis in a new joint; this was noticed soon after admission. There was no increase in symptoms either objectively or subjectively.

The respiratory metabolism was studied in seven of the cases. In six it was followed throughout the period of observation at frequent intervals. We anticipated that the initial metabolic rates would be reduced as a result of their undernourished state. Only one patient, Case 1, did have a temporary slight lowering of the rate early in the study, which was possibly due to an antecedent respiratory infection. Also, these rates were found to be steady throughout the period of observation and to be uninfluenced by increasing body weight.

The trend of the postabsorptive respiratory quotients, even though they showed in some cases rather wide variations, was approximately level throughout. The quotients during the periods of insulin administration were not altered. The average quotient was found to be slightly higher than that of individuals who eat the ordinary mixed American diet.

It then seems that the seven patients with advanced chronic atrophic arthritis, upon whom postabsorptive respiratory quotients were determined while they were taking a high carbohydrate diet, were able to use carbohydrate normally.

We do not, however, believe that a high carbohydrate diet has any special efficacy in the treatment of chronic atrophic arthritis, but we do stress the importance of overnutrition in the management of such patients when they are undernourished.

This study would not have been possible but for the untiring cooperation of the hospital dietitian, Miss Dorothy Lowe, her assistant, Miss Eve Vogel, and the laboratory assistants, Miss Grace E. Sly and Miss Rachel Walker.

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DISCUSSION

DR. CHARLES W. SCULL, ELKINS PARK, PA.—Drs. Bowen and Lockie have added significant data to the chapter on the dynamic pathology of arthritis in reference to carbohydrate metabolism. The conclusion that the undernourished arthritic patient uses carbohydrate normally may at first thought appear to be inconsistent with the fact that many arthritic patients show a delayed rate of removal of glucose when submitted to a tolerance test. However the "diabetic-like" response of the arthritic patient may be referable to circulatory disturbances rather than to an inherent deficiency of carbohydrate metabolism. The present data indicating an essentially normal respiratory quotient and a negative effect of insulin upon the nutrition of the arthritic patient lend further probability to this view.

The present observations also focus attention upon the influence of nutrition on clinical progress with particular regard to caloric balance and the qualitative composition of the diet. Drs. Bowen and Lockie studied severely undernourished patients. Measures to cor-

rect this state of relative starvation are obviously indicated. One of the first requisites toward this end is a caloric supply in excess of the energy output. The desideratum, however, is not merely the storage of calories in the form of fat, but the achievement of a state of optimal nutrition. The problem of restoring nutritive balance in a malnourished arthritic patient is not a simple matter of providing an abundant supply of calories in the form of any one foodstuff. The correction of gross malnutrition involves as many factors as are involved in the growth process. Either absolute or relative deficiencies of any of the dietary components which are not interchangeable with one another may constitute limiting factors to normal growth. If insufficient iron is supplied, hemoglobin cannot be produced; if calcium or phosphorus be lacking, normal ossification does not occur; if iodine is lacking, thyroxin cannot be produced; if essential amino acids are inadequate in amount, the protein structural units of tissue, viz., muscle, the organic matrix of bone, tendons and cartilage cannot be elaborated. A net loss of these essential factors from tissues in disease leads to structural collapse. On these premises it is apparent that a high carbohydrate supply alone cannot be expected to correct malnutrition, to compensate for amino acid deficiencies or replace inorganic salts, essential fatty acids, or accessory food factors.

These considerations are of more than academic importance. Drs. Bowen and Lockie have recorded the fact that three of the eight patients even while receiving an adequate supply of calories in the diet failed to make striking progress so far as the arthritis and nutritional state were concerned. While in them factors other than dietary may have prevented progress, attention may be called to the fact that some selected cases on the high carbohydrate, high caloric diet equilibrated with respect to bed rest, removal of foci, etc., may experience a marked benefit when the diet is changed to one richer in protein, fat, vitamins, and salts. Several explanations have been advanced to account for this effect. It has been noted in our laboratory and by Adlersberg and Porges in Germany that such dietetic changes are accompanied by a loss of fluid from the body along with a reduction of tissue swelling. Pevsner and other Russian investigators have noted that such a dietetic alteration is accompanied by a reduced sensitivity of the arthritic patient in an allergic sense.

Irrespective of the mechanism whereby such dietetic differences become effective they emphasize the fact that some practical approximation of a dietary prescription may be made which provides not merely a tolerable, not merely an adequate, but an optimally constituted mixture out of which the body may maintain, repair and build its tissues and function at a level approaching optimal physiology. Some arthritic patients may get well in the presence of infected teeth, or tonsils; some may improve in spite of the handicap of suboptimal diets, but more will get well more rapidly if given the benefit of judicious removal of foci and the application of dietetic measures.

DR. T. PRESTON WHITE, CHARLOTTE, N. C.—Dr. Bowen has used for observation eight cases of atrophic arthritis of some years' duration. As was to be expected, the improvement shown depended on the activity and stage of the disease; inflamed swollen joints are capable of great improvement, whereas, stiff, cold, burned-out joints can hardly be benefited. The observation that the patients gained weight no faster on insulin than without it, is interesting. The effect of the high carbohydrate, low protein and fat diet on articular pathology can only be said to be a negative one. Only one new joint became involved and the old ones did not become worse.

The improvement noted in about one-half of his cases may have been due in some measure to the greater supply or the greater utilization of carbohydrates, but it is just as reasonable to attribute improvement to the forced eating of the remainder of the diet, to prolonged bed rest, or to proper elimination.

The rôle of diet in arthritis is still unknown. The difficulty lies in controlling the many other factors while the effects of various diets are being studied. In our experience patients suffering with atrophic arthritis do best when treated as a whole, placing them on a balanced diet that would restore the weight to a normal level, giving the patient complete rest, and paying the closest attention to the question of bowel elimination. Physical therapy is a most helpful aid.

The improvement obtained by our patients seems to be directly in proportion to the amount of rest and to the careful attention to elimination. When the disease has become

arrested, patients eat what they want. Those patients who have stayed well over a long period of time have told me that rest and elimination are the most important factors from their standpoint. In my part of the country most people are big bread eaters and because of the quantity of bread consumed they do not eat enough vegetables and fruits. Most of these people are definitely benefited by curtailing their carbohydrate intake and insisting on more fruits, vegetables, and red meats.

We may well take a leaf from the book dealing with the treatment of tuberculosis, and in the beginning, stress to the patient suffering with arthritis the importance of the length of time which it takes to arrest it, and, when it becomes arrested, that he must lead a life which does not permit exhaustion, and that he will never be able to go at the same pace as those people who have not been affected by the disease.

DR. PHILLIP S. HENCH, ROCHESTER, MINN.—Drs. Bowen and Lockie are not proposing a new diet for the much-dieted arthritic patient. Admitting that there is no special efficacy to a high carbohydrate diet for atrophic arthritis they have, however, shown that such a diet is apparently quite harmless. One is permitted to conclude that they believe that restrictions in carbohydrate intake have no particular merit either.

When one studies patients with atrophic arthritis intensively, one finds physiologic aberrations pertaining not only to carbohydrates, but also to sulphur, cholesterol, perhaps to calcium, and other substances. The apparent disturbances in carbohydrate metabolism, which, by the way, are by no means consistently present, have not seemed to me to be of greater significance than other alterations and the rationale for a low carbohydrate diet in the treatment of atrophic arthritis has not been proved to my satisfaction. Nevertheless, when such a diet was proposed again several years ago we gave it a trial in about two hundred cases with, in general, disappointing results. Very few patients whose relief is ascribed to a low carbohydrate diet are actually treated by that means alone. Most of them have also had some infected focus removed, are given physiotherapy, and certain extra amounts of rest in a hospital or at home.

At the Mayo Clinic, we have abandoned the use of a low carbohydrate diet as a routine measure although we are quite willing to prescribe it to a patient who insists that carbohydrates make the joints worse. However, one often finds on quizzing such a patient, that she never noted a relationship until she read in a health column, or was told by her physician, that she should avoid carbohydrates. When later she ate some, it was perhaps her conscience more than her joints that hurt. A shifting barometer may unwittingly have provided increased pain coincident with her dietary "indiscretion." At any rate, we have found the stories of such, patients very inconsistent. They blame one carbohydrate-containing food, not another which contains equal amounts. They note joint pains after eating carbohydrates in one form but not when they eat the same carbohydrate-containing food in another form. We have not been able to convince ourselves that any one type of carbohydrate or carbohydrates in normal or even excess amounts, are specifically harmful.

Apropos of the apparent harmlessness of a high carbohydrate intake, you may recall that two years ago, before this conference, I reported on the analgesic effect of jaundice in certain rheumatic diseases. I have now studied about forty patients with atrophic arthritis and fibrositis, whose disease was largely or completely inactivated by various types of jaundice. While these patients were in the hospital under the care of Drs. Snell, Weir, Comfort, and myself they were routinely given 400 to 500 gm. of carbohydrate daily (bread, cereals, potatoes, crackers, jellies, cakes, fruit juices and candy between meals). They were on this diet three to five weeks in the hospital, and at least three to six months thereafter. While in the hospital they were generally given also an average of 100 gm. of sugar intravenously, daily for three weeks. Glycosuria was often produced but the analgesia and reduction of stiffness and swelling of joints were in no way disturbed by this intake of 400 to 600 gm. of carbohydrate daily for many weeks.

DR. BOWEN (closing).—I neglected to speak of the difficulty we experienced in getting our patients to eat even the rather low protein content of their diets. The amount that they actually ingested was usually 5 to 10 gm. lower in protein than was served them.

THE PRESENT STATUS OF FEVER THERAPY IN THE TREATMENT OF GONORRHEAL ARTHRITIS, CHRONIC INFECTIOUS (ATROPHIC) ARTHRITIS, AND OTHER FORMS OF "RHEUMATISM"*

PHILIP S. HENCH, M.D., ROCHESTER, MINN.

VARIOUS methods for the production of fever in "fever therapy" include diathermy; radiothermy; heated, air-conditioned cabinets; hot baths, and heated air currents. Regardless of the method used, certain, and at times rather profound, physiologic effects are produced. These include alterations in the blood flow, in the chemical and cellular elements and immune bodies of the blood, in the content of sweat and gastric secretions, in the amount and reaction of urine, in the metabolic rate, and in electrocardiograms. Some of the reactions are of little consequence either from the standpoint of discomfort or relief. The most important are the effects of therapeutic hyperpyrexia on the growth of invading organisms, such as the bacteriolytic and bacteriostatic effect of fever therapy on gonococci and on the spirochete of syphilis.

Since 1931, fever therapy has been used in the treatment of various "rheumatic diseases," with striking success in the gonorrheal type and with moderate success in other types. Twenty reports on the results of fever therapy in gonorrheal arthritis have been made in this country: ten have been published, and the reports have been summarized by Hench, Slocumb and Popp,¹ and ten were given at the Fifth Fever Therapy Conference in Dayton in May, 1935^{2, 3} (Table I). Twenty reports on results in acute and chronic infectious (atrophic) arthritis have likewise appeared: sixteen have been published¹ and four were made at the recent conference^{2, 3} (Table II). There has been a considerable variety in the methods used, in the dose of fever, and in the number of sessions of fever given. The results have varied considerably in earlier reports, less so recently. An analysis of results does not suggest that one method is superior to another so far as results in the diseases treated are concerned, and a choice of method resolves itself into the selection of that one which is the most comfortable, the least dangerous, and the least expensive to the patient. The majority of workers to date seems to favor the use of heated, air-conditioned cabinets, such as the Kettering hypertherm. The use of such cabinets seems to be less exhausting than hot baths or diathermy hyperpyrexia, and less expensive and less likely to produce cutaneous burns than radiothermy. The oral administration of 3 to 4 liters of 0.6 per cent solution of sodium chloride during the sessions of fever markedly reduces unpleasant reactions.

Gonococci are generally killed by five to seventeen hours of fever at 106.7° F. (41.5° C.); a few hardy strains are killed only after twenty-seven hours of such a fever. Since these amounts of fever can be equalled or exceeded in a single or in divided doses in the treatment of patients, the effect of fever therapy

*From the Mayo Clinic.

TABLE I
FEVER THERAPY FOR GONORRHEAL ARTHRITIS: REPORTS AT FIFTH FEVER THERAPY CON-
FERENCE, MAY, 1935

AUTHOR	DOSE OF FEVER RECOMMENDED; HOURS AND DE- GREES F.	TOTAL NUMBER SESSIONS OF FEVER	PATIENTS TREATED	RESULTS, PER CENT				AUTHORS' COMMENTS
				SYMPTOM- FREE; "CURED"	MARKED RELIEF	MODERATE RELIEF	LITTLE OR NO RELIEF	
Warren, Car- penter and Boak	5 to 17 hr. at 106.7°	1; equal to ther- mal death time of pa- tient's strain	15	87	*	*	*	Patient may be infected with two strains; that of patient and con- sort generally about equal. Strains from urethra and joints may have different thermal death time (usually a little shorter from joints)
Stecker Bierman	*106°	1 to 2+	18 16	61 81		33 6	6 13	Complete cure if bony changes not present. Physiotherapy for residual stiffness
Hefke	5 to 6 hr. at 105 to 106°	3	4	100				
Arnold Lepore Schnable	*106 to 107° 5 hr. at 106 to 107°	* 2 to 6	19 6 Acute 9 Chronic 9	89 100 56	11			Results remarkable
Tenney Strickler	6 to 7 hr. at 105 to 107°	* 4	3 Acute 9 Chronic 4	100 45	33	11		In acute cases, results "striking" to "miraculous"
Kendell and Webb	6 to 7 hr. at 106 to 107°	*	Acute 19 Chronic 12	84 41	22 *	22 *	11 25 *	No better than other treatment
Total			143	About 72 per cent	About 8 per cent	About 20	per cent	

*Data incomplete.

TABLE II
FEVER THERAPY FOR INFECTIOUS ARTHRITIS: REPORTS AT FIFTH FEVER THERAPY CONFERENCE,
MAY, 1935

AUTHOR	DOSE OF FEVER RECOMMENDED; HOURS AND DE- GREES F.	TOTAL NUMBER SESSIONS OF FEVER	PATIENTS TREATED	RESULTS, PER CENT				AUTHORS' COMMENTS
				SYMPTOM- FREE; "CURED,"	MARKED RELIEF	MODERATE RELIEF	LITTLE OR NO RELIEF	
Stecker	3 hr. at 103 to 104°	1 to 4	Acute 13 Chronic 33		46 33	31 27	23 40	If no relief with first session, treatment discontinued No better than other treatment; temporary relief of pain Two patients had diabetes; not considered a contraindication
Strickler	6 to 7 hr. at 105 to 107°	4	Acute 8	25		50	25	
Hefke	103 to 105°	4 to 5	Chronic 31 Early 10	7	60	58	35	
Tenney	3 to 4 hr. at 104 to 106°	*	Late 13		23	23	20	
			21	"86 per cent improved,"				
Total			129	About 7 per cent	About 30 per cent		14	

* Data incomplete.

* Data incomplete.

in gonorrheal arthritis is apparently to sterilize the joints through a direct bacteriolytic effect. The usual plan of treatment is to give two to six sessions of fever at 106° to 107° F., for five to six hours. Recently, Warren, Carpenter, and Boak have proposed an alternative plan in cases in which the thermal death time of the infecting strain of gonococci can be determined: one prolonged session (five to seventeen hours) is given, which is equivalent to the thermal death time (at 106° to 107° F.) of the patient's particular strain. This method may be less expensive and is of course less time-consuming; it may not, however, be practical for other than selected cases.

RESULTS IN ACUTE GONORRHEAL ARTHRITIS

In spite of growing conservatism in estimating the results, those obtained in gonorrheal arthritis are striking. In acute gonorrheal arthritis the results have been as follows (figures are given in round numbers and are therefore approximate; percentages for those receiving less than notable or marked relief are omitted here): Of the first 24 patients treated (reports published earlier, from various sources), 90 per cent were promptly cured and 10 per cent received little or no relief. Of 118 cases discussed at the recent conference, 80 per cent of the patients became symptom-free, 10 per cent were markedly relieved, and 10 per cent but slightly relieved. Of 9 patients treated at the Mayo Clinic, 5 were promptly cured, the rest markedly relieved. Thus, of a total of 151 patients with acute gonorrheal arthritis, treated by a number of different physicians in various parts of the country, 80 per cent have apparently been cured and an additional 10 per cent have been markedly relieved (Table III).

RESULTS IN CHRONIC GONORRHEAL ARTHRITIS

The results in chronic gonorrheal arthritis (of more than six weeks' duration), while very good, are less striking (Table III). In 25 cases reported at the conference, 40 per cent of patients were "cured," 30 per cent markedly relieved. In 7 from the Mayo Clinic, 25 per cent were cured, 45 per cent markedly relieved. Thus of a total of 32 patients, 35 per cent were cured and 30 per cent were markedly benefited.

RESULTS IN ACUTE INFECTIOUS (ATROPHIC) ARTHRITIS

Doses of fever available in fever therapy are inadequate to kill the streptococci presumably responsible for acute and chronic infectious (atrophic) arthritis. Such results as are obtained arise presumably from possible bacteriostasis, augmentation of the patient's resistance, and vasodilatation. The usual plan is to give three to eight sessions of fever at 104° to 105° F. for about four to five hours. Of 21 patients with acute (nonspecific) infectious arthritis whose cases were reported at the conference, 10 per cent only were "cured" but an additional 40 per cent were markedly relieved (Table III).

RESULTS IN CHRONIC INFECTIOUS (ATROPHIC) ARTHRITIS

Of a total of 147 patients with chronic infectious arthritis previously reported on by a number of physicians, 10 per cent became symptom-free, 25 per

cent were notably benefited. Of 108 patients reported on at the conference by several workers only 5 per cent became symptom-free but an additional 30 per cent were notably relieved. At the Mayo Clinic, 60 patients have been treated;

TABLE III

FEVER THERAPY--SUMMARY OF RESULTS TO DATE (PERCENTAGES ARE GIVEN IN ROUND NUMBERS AND ARE THEREFORE APPROXIMATE)

DISEASE	PATIENTS TREATED	RESULTS, PER CENT			
		SYMPTOM-FREE; "CURED"	MARKED RELIEF	MODERATE RELIEF	LITTLE OR NO RELIEF
Gonorrheal arthritis, acute	Published	24	90		10
	Conference	118	80	10	10
	Mayo Clinic	9	50		
	Total	151	80	10	
Chronic (more than 6 weeks)	Published, undifferentiated from above				
	Conference	25	40	30	30
	Mayo Clinic	7	25	45	15
	Total	32	35	30	
"Infectious arthritis" (atrophic) acute	Conference	21	10	40	50
	Published	147	10		
	Conference	108	5	30	65
	Mayo Clinic	60	0	20	60
Chronic	Total	315	5	25	
	Published	74	5	50	45
	Published	1	100		
	Published	2	100		
Senescent arthritis (hypertrophic)	Published	6	80	20	
Gouty arthritis (chronic)	Published	8	25	75	
Traumatic arthritis (chronic)	Published	4	50	50	
Neuritis	Published				
Myositis	Published				
Bursitis	Published				

none was cured, 20 per cent considered themselves, and were considered, to be markedly benefited. Thus of a total of 315 patients treated in different clinics, 5 per cent became symptom-free and 25 per cent were markedly relieved. The remainder received little or no benefit (Table III).

A very few patients with senescent (hypertrophic), chronic gouty, and chronic traumatic arthritis, as well as a few with neuritis, myositis, and bursitis, have been so treated. Those with senescent arthritis have not been particularly benefited except in a few instances. From 25 to 50 per cent of those with the other types of arthritis have been reported as notably helped (Table III).

CONCLUSION

From the results collected from various parts of the country to date, one may tentatively conclude that, if early and adequate treatment is given to a patient with gonorrheal arthritis, he has an 80 per cent chance of being promptly cured, and if not cured an additional 10 per cent chance of being markedly relieved. The treatment is almost specific, and it is almost completely successful when bony changes have not occurred. A patient whose gonorrheal arthritis is

of more than six weeks' duration has lost valuable time. Even so, such a patient has a 35 per cent chance of being more or less promptly cured, and if not cured, then a 30 per cent chance of being markedly relieved. Physiotherapy may be needed for residual stiffness. Ankylosis may persist. In any event, fever therapy is the method of choice and in any case of acute gonorrheal arthritis it should be promptly instituted.

In infectious (atrophic) arthritis, results are often gratifying, occasionally striking, but in general disappointing. The patient with acute infectious (atrophic) arthritis has a 10 per cent chance of becoming symptom-free, a 40 per cent chance of receiving notable relief. The patient with chronic infectious (atrophic) arthritis has only a 5 per cent chance of becoming symptom-free, a 25 per cent chance of being notably helped. A welcome remission may be induced. A "cure" is not to be expected. The best results are obtained when the disease is of less than a year's duration. Further experience is necessary to determine the exact value of this treatment in chronic infectious arthritis. It can hardly be considered successful in cases in which patients receive only moderate relief, for such relief can be obtained almost routinely by less expensive and less strenuous methods of treatment. For patients inadequately relieved by other measures, or who are intolerant of slower methods, a trial of fever therapy seems justified.

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DISCUSSION

DR. W. J. STAINSBY, NEW YORK, N. Y.—Every year for years several forms of therapy have been advocated with enthusiasm for the cure of either gonococcal or more particularly, atrophic arthritis. With few exceptions after the period of enthusiasm has subsided these new forms of therapy have been discarded. One of these exceptions is the removal of foci of infection. Many years ago Billings pointed out the relation of foci of infection to arthritis. After a period of enthusiasm in which many innocent teeth and tonsils were removed, the value of this form of therapy took its proper place. At the present time we recognize it as being of distinct value in a limited group of patients with arthritis. However, as far as the large majority of patients is concerned, this form of therapy is not of much use. More recently we have had a wave of enthusiasm over vaccines. Various forms of vaccines were used for a period of about ten years. After the wave of enthusiasm subsided many arthritic specialists were not so enthusiastic about the improvement, and no definite evidence is at hand that vaccines definitely modify the course of the disease. That applies to gonorrheal arthritis as well as atrophic arthritis. I am speaking of permanent cures, not temporary relief. There are of course many measures that temporarily relieve the symptoms. With this background you can see why I view with some skepticism the recent wave of enthusiasm about fever therapy.

Dr. Hench's results correspond with the reports of other investigators with this form of therapy in gonococcus arthritis. I would like to consider all these reports as preliminary and wait for more definite evidence of the value of this form of therapy in gonococcus arthritis.

Dr. Hench's results in atrophic arthritis are much less striking. They correspond with our own. In 1933 Nicholls, Hansson, and I reported 12 patients treated with this form of

therapy. In all cases there was temporary relief of the symptoms, but at no time did we find that this form of therapy cured the disease.

In my opinion this form of therapy in gonorrheal arthritis is promising at the present time, but is of no use in the treatment of atrophic arthritis.

DR. WALTER BAUER, BOSTON, MASS.—Dr. Charles L. Short and I began the treatment of patients with arthritis by means of hyperpyrexia the latter part of 1930. We wish to reemphasize what Dr. Hench has said concerning the value of this treatment in gonorrheal arthritis. It is the nearest thing to a specific therapy that has ever been employed for this type of arthritis. Our certainty regarding the value of this form of therapy in gonorrheal arthritis has been based on the thorough studies of Dr. Stafford Warren and his group at Rochester. Without their detailed bacteriologic studies on the thermal death point of various strains of gonococci, we would be unable to prescribe treatment intelligently or properly to interpret the results.

The results obtained in treating atrophic arthritis with hyperpyrexia are not very encouraging when compared with those obtained in gonorrheal arthritis. We have treated a total of 25 cases of atrophic arthritis with a total of 71 treatments. Following one or more treatments by means of a Victor superpower diathermy machine and electrodes, the patients were observed for a period of one to three years or more. The number of treatments given each patient varied from one to fifteen and the usual temperature maintained was 104° for four hours.

In 20 out of our 25 cases, temporary improvement resulted both subjectively and objectively. The results were at times almost miraculous, but unfortunately of very short duration. In only 5, or 20 per cent, was this gain maintained to the end of the follow-up period. The end-results are best shown in table form.

DURATION OF IMPROVEMENT

DURATION	CASES
None	5
Up to 2 weeks	8
From 2 weeks to 6 months	6
From 6 months to 1 year	1
From 1 year to 2 years	2
Two years or more	3

Of the 5 patients who improved, one become pregnant within a month after her last treatment and has continued free of pain. It is known that pregnancy may induce a remission in atrophic arthritis. In another patient, a remission apparently had started two months before the treatments were begun. A third patient has pursued an unusually faithful course of rest and physical therapy at home. Therefore, in three of the five patients who received benefit, it is not possible to ascribe the entire improvement to diathermy hyperpyrexia. Those who improved were younger, their arthritis of shorter duration with little or no cartilage destruction and two had marked vasomotor symptoms.

Therefore, balancing the results obtained against the severity of the treatment, our conclusion is that in atrophic arthritis, the use of this method is only occasionally justified and should not be used to the exclusion of general treatment.

DR. ROBERT B. OSGOOD, BOSTON, MASS.—I believe it is the informed and wise opinion of the people who have tried it, as Dr. Hench and Dr. Bauer well know, that this form of treatment should only be administered in a well-equipped hospital with attendants who are trained in its use. If this method were generally used, I think we should expect some disastrous results.

DR. R. GARFIELD SNYDER, New York, N. Y.—May I reemphasize Dr. Osgood's warning? I think fever therapy is a very dangerous form of treatment, and should be used only in heroic cases when everything else has failed to bring about improvement. I have had

one case of gonorrheal arthritis in which this method of treatment was used with a fatal outcome. The treatment was carried out at the hospital and the patient's temperature was elevated to 104° F. Soon after completion of the treatment the patient's temperature rose to 106° F. then to 107° and death followed. There seemed to be no explanation for what occurred, except that the rise of temperature induced by the fever treatment continued progressively through some unexplainable loss of control in the temperature controlling center of the brain.

DR. WALTER M. SIMPSON, DAYTON, OHIO.—High, sustained, controlled artificial fever is the treatment of choice for gonorrheal arthritis. Gonorrheal arthritis is a manifestation of a systemic disease, requiring systemic treatment. In vitro thermal death time studies, and the clinical response of patients with gonococcal infections to artificial fever therapy, indicate that it is possible, in most instances, to destroy gonococci in the various lesions of the disease with high, sustained body temperature. In addition to this sterilizing effect, there is evidence that artificial fever therapy stimulates immune reactions.

Thirty-one patients with gonorrheal arthritis, associated with gonococcal infection of the genitourinary tract, have been treated by us with artificial fever therapy, utilizing a simplified, relatively safe and controllable air-conditioned apparatus, known as the Kettering hypertherm. Of 19 patients with acute gonorrheal arthritis the average improvement in joint function immediately after the conclusion of the course of fever therapy was 75 per cent; in three patients the restoration of joint function was complete. The ultimate average improvement in joint function in the cases of acute gonorrheal arthritis was almost 100 per cent; 13 patients have obtained complete restoration of joint function. Of the 12 patients with chronic gonorrheal arthritis the average improvement in joint function at the conclusion of the course of fever therapy was about 60 per cent; in 4 patients joint function was completely restored. The ultimate improvement in joint function in cases of chronic gonorrheal arthritis was almost 90 per cent. At the conclusion of the course of fever therapy gonococci had disappeared from the smears of the genitourinary tract of 24 patients. The urethral smears of 4 patients became negative within a week following the conclusion of the fever treatments. Supplemental treatment eliminated all evidence of gonococcal infection of the genitourinary tract of the remaining 3 patients.

In 2 cases of chronic gonorrheal arthritis almost complete limitation of motion of one knee joint remained after the conclusion of the course of artificial fever therapy. Orthopedic manipulation (*brisement forcé*) under general anesthesia was done to separate fibrous adhesions. Artificial fever therapy was reinstituted immediately following the surgical manipulation. Practically normal joint function has been restored in both cases.

WHAT CAN BE EXPECTED FROM THE ORTHOPEDIC CARE OF ARTHRITIS?

LORING T. SWAIM, M.D., BOSTON, MASS.

I AM not going to discuss the treatment of arthritis except to try to bring to your attention what can be expected from orthopedic care in chronic arthritis. The word orthopedic means "straight child." Nowhere in the practice of orthopedic surgery is the name more truly exemplified than in chronic arthritis because it is so vitally important that every patient with chronic arthritis should be properly balanced mechanically after he is well. Many patients with arthritis have been cured of the active disease but have been so crippled that they could do nothing. They might just as well have not got well. There must be complete understanding between the medical and the orthopedic physicians in every case of arthritis. In order to have successful results in arthritis, each physician must know exactly the plan of the other and what can be expected from cooperative treatment. What can the medical man expect from his orthopedic confrere?

He can expect the prevention of the flexion deformities, if early protective splinting can be started before the deformities have occurred. This means consultation at the very beginning of the arthritis. It means careful observation of the joints at frequent periods to size up the tendencies in each joint, and anticipate the probable deformities which are likely to occur or are occurring. Joint deformities begin very early during the inflammatory period of rheumatoid (atrophic) arthritis. This must be appreciated by whoever is in charge of the case; otherwise the pain with resulting muscle spasm and flexion will insidiously produce deformity. At first this does not seem of great significance. It is at this time that the deformity can be prevented most easily. Complete rest of the joint for a period of a few days to a week is often sufficient to cause a complete subsidence of the acute inflammatory reactions. Pain, so often due to slight, continued trauma of motion, can be entirely eliminated by complete rest in a plaster cast. It is difficult for us to realize how much trauma actually takes part in the production of inflammation in chronic arthritis. I firmly believe that at least 50 per cent of the inflammation in joints is kept up by use during the acute stages of the disease rather than by the actual etiologic factor, whatever it is. I also believe that a great deal of the capsular thickening and the extension of pannus between the surfaces of the joint would be less if trauma were prevented. This has been our experience in the protection of joints in the last eight years. Constant attention to details, with the use of plaster casts and shells for rest, we have found, has lessened danger of ankylosis and stiffening of the joints more than where the joints are not protected and rested. Exercise is all right at certain times in small amounts, but the time for motion must be carefully chosen, and during the time of exercise the joint must be under constant supervision and the pain and spasm reactions noted.

Another thing which I think it is hard for us to realize is that the use of supports must be continued over considerable length of time even after it seems unnecessary. The after-care of chronic arthritis is almost more important, if it is conceivable, than the treatment during the active stage. I am sure that if the acute joints are treated by complete rest, pain, swelling, and permanent damage are decreased. I think that those who have tried this protective rest method of splinting will agree that far less analgesics are necessary where joints are protected and the mental hazard of pain is eliminated to a large extent.

The second benefit which we may expect from orthopedic treatment is that many of the early contraction deformities of the joints can be straightened out without surgical interference, if corrective splints are used. The same method as is used in the prevention of deformity can be carried out over a period of time, if a series of corrective supports are used.

The chief cause of flexion is pain. Pain causes spasm. Spasm causes contraction of the muscles in an attempt to immobilize the joint. If rest is artificially secured, the necessity for spasm is eliminated. The joint relaxes and inflammation subsides if it has not become too great, the spasm lets go and the deformity is corrected. If deformity has already started, it still is not too late to expect some correction by rest and protection, so that orthopedic consultation at this time is still important.

Third, operative procedures to restore functional use of the joints can be instituted with a fair degree of success. Many times there has been a good deal of skepticism as to the possible correction of deformities by operative means. We have been taught that operation was dangerous in arthritis and was rarely successful. I think the reason for this is that we have not operated at the right time; we must wait for the disease to subside, however, and until the patient is able to stand the operation. It has been my experience that operations on arthritic patients were perfectly possible and no more dangerous than in other patients. There seems to be no more likelihood of ankylosis or infection or of lack of bone union in chronic atrophic arthritis than in any other disease, provided the operation is performed after the disease has been quiescent for at least three or four months, longer, if possible, or when the patient has developed a sufficient resistance to the disease and is gaining weight, strength, and vitality. I think it is as wrong to operate on a patient with chronic rheumatoid arthritis orthopedically, as it is to remove a focus of infection at the wrong time and in a state of depleted resistance. One of the operations which has been most successful in correction of deformity in chronic arthritis is synovectomy, for the removal of the synovial tissue which blocks the joint motion. Just as a semilunar cartilage prevents complete extension, so the synovial tissue, being sensitive, produces pain when pinched, and results in flexion. Good motion is often secured by its removal. There are certain dangers in this type of operation, and it is indicated only in a limited number of cases where the anterior part of the knee under the patella in the suprapatellar pouch is filled with masses of inflamed synovial tissue and pannus. There is danger of limited flexion due to adhesions under the patella.

Arthroplasties are often quite successful in elbows and knees but not so good in hips, shoulders, and fingers. They are indicated where the joints are ankylosed. Good results are usual in elbows and knees. The third operation, the posterior capsuloplasty of the knee, may be very successful where the knee is flexed, only partly subluxated, and where the posterior capsule is very thick, indurated, and too tight to be stretched by manipulation to allow the knee to come out straight. It gives exceedingly stable, straight knees with usually increased range of motion.

The reeducation of muscles should be undertaken prior to operation in order that motion may be secured as soon as possible after the operation. Physical education is vitally important in the after-care of the chronic arthritic, because in walking it is essential that the body be so balanced that there is the least amount of strain on the joints of the legs. This means corrective posture work in order that the trunk may be used normally, that the strain on the hips and knees and feet is the least possible, and particularly that the strain on the neck and back is eliminated. Only through putting the body in the best possible condition can we expect to keep the resistance of the chronic arthritic patient at the high level, prevent the strain on the joints, and prevent recurrence of symptoms.

Flat feet, bent knees, flexed hips—all produce strain and result in back, shoulder, and neck strain. A deformed body is always lacking in resistance. It is true of lateral curvature and is true in arthritis. We have never succeeded in securing satisfactory use of flexed knees. It has always caused trouble sooner or later. A lordotic back always causes pain some time, and strains other joints. Therefore arthritic patients, because of their joint damage, must be particularly protected from strain.

DISCUSSION

DR. A. R. SHANDS, JR., DURHAM, N. C.—The problems which the orthopedist has to meet would be less serious ones if arthritic patients were examined and treated early. The plea which Dr. Swaim is making to the general practitioner is to refer patients for orthopedic care before crippling deformities occur. I am convinced that 75 per cent of the orthopedic work in the correction of deformities in arthritis would be unnecessary if preventive medicine were practiced. In the treatment of these cases the physician must have a tremendous amount of patience and optimism, but the arthritic patient is the most grateful individual for the relief of pain and for the least improvement in joint function.

At the Duke Hospital we have felt that in some patients with contracted knees and elbows a manipulation or stretching of the joints can be accomplished with less force and a greater number of knees can be straightened after fever therapy much more easily than would be expected without this treatment. We have felt that the excessive heat had a softening effect upon the adhesions. Our experience in the treatment of atrophic arthritis has been that very seldom is there permanent relief of symptoms following fever therapy alone.

Dr. Swaim is to be congratulated upon the most excellent results obtained in the treatment of these patients he has shown.

DR. DENIS S. O'CONNOR, NEW HAVEN, CONN.—Dr. Swaim represents the ideal practitioner to handle arthritis. Essentially an internist, he has the viewpoint of the internist, but with his orthopedic training, he is competent to handle the joints themselves while he is bringing the arthritic disease under control. The viewpoint of the internist and the training of the orthopedist in one practitioner is what is needed for the most effective handling of arthritis.

The problem might be divided into the treatment of the disease and protection of the joints. The disease may be, but is not necessarily, mainly in the joints. The effects of the disease are very definitely in the joints.

Arthritis is a medical problem and becomes an orthopedic problem only if the medical attendant fails. Arthritis is an orthopedic problem from the beginning if prevention of deformity logically comes within the province of the orthopedist. There can be no dispute as to the province of the case if the internist is capable of caring for the joints, and it would seem to be within the scope of this Association to survey the teaching of orthopedics in our medical schools to see if the medical practitioner is being taught the basic facts pertaining to joints.

Trauma in relation to arthritis cannot be overemphasized. In true infectious arthritis trauma is frequently the localizing factor. In hypertrophic arthritis, it is an essential etiologic factor. In toxic arthritis it is a sustaining factor. Trauma must be thought of in its widest sense and may be classified as "physiologic," meaning the trauma of physiologic use; "occupational," meaning the trauma which arises from the repeated use of a joint in occupation; and "accidental," representing that violent form which the word trauma usually connotes.

Theoretically the optimum position of use of a joint, or correct posture, would result in a minimum trauma to the joint but you all know how infrequently the physiologically correct posture is met with in daily life.

The flat feet, the bent knees, the exaggerated spinal curves, the sagging shoulders are faults of posture producing strains. Muscle training with the help of corrective supports will prevent the fixed deformities which usually call forth surgical measures.

THE TREATMENT OF ATROPHIC (RHEUMATOID) ARTHRITIS WITH LEUCOCYTE CONCENTRATE*

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THE administration of whole human leucocytes by subcutaneous injection in atrophic (rheumatoid) arthritis patients was suggested to us on theoretical grounds. These theoretical considerations, the method of preparation of the leucocyte concentrate and the results of this type of treatment are presented below.

The research of the last thirty-five years in atrophic (rheumatoid) arthritis tends to show that two factors are operating. One is infection, and the other a fundamental constitutional derangement which allows the infection to produce its characteristic effects. The details of these two factors are still matters of continued dispute.

In the face of undoubted evidence that infection plays an important rôle in atrophic (rheumatoid) arthritis, we find very little change in the circulating leucocytes. It is agreed that the typical blood picture in chronic arthritis is as follows: a slight secondary anemia, a normal leucocyte count, a normal neutrophilic ratio but an increase in the proportion of young, nonfilamented neutrophils, causing a nuclear shift to the left, and in many cases a tendency to lymphocytosis.¹⁻⁴

If infection plays a large rôle in atrophic (rheumatoid) arthritis, it is obvious that the leucopoietic functions of the body do not respond in the usual way. The hemopoietic function is likewise depressed. Anyone with experience in the treatment of arthritis has noted how resistant are the low red blood cell count and hemoglobin to the best possible constitutional treatment. This lack of response on the part of the bone marrow may be due to the effect of some toxin, or, in the case of the leucocytes, to the fact that whatever infection is present in atrophic (rheumatoid) arthritis is so low in virulence that it does not stimulate the bone marrow. Another possibility is that there is a fundamental hormonal deficiency in atrophic (rheumatoid) arthritis of a type simulating the deficiency in pernicious anemia. As far as I know no study of the bone marrow in arthritis has ever been published.

In recent years a great deal of the therapy in arthritis and other apparently infectious diseases of low virulence, has taken the form of injections of heterogeneous substances to produce what is called the nonspecific protein reaction. The most marked characteristic of the reaction is the leucocytosis and neutrophilia. Even the administration of the so-called specific vaccines has this concomitant effect, and it is suspected by many that their sole value

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is in this reaction. While the nonspecific protein reaction is frequently beneficial, it rarely proves curative, and so other methods to stimulate the myelopoietic function have been sought.

One of these is the administration of nuclein. Nuclein has been used to stimulate bodily resistance since 1893,⁵ at first empirically. A rational basis for this use was laid by Jackson⁶ in 1924, who demonstrated the existence of pentose nucleotides in normal human blood. Subsequently it was shown by Doan and his coworkers⁷ that nucleic acid and its derivatives stimulate the myelopoietic function of bone marrow in rabbits. Doan attributed to these substances qualities of chemotactic, maturative and initiatory stimuli for neutrophilic myelocytes, when the basic mesenchymal tissues from which they arise are in a condition to respond.⁸

Doan and others in 1928⁹ and again in 1932⁸ summarized the situation to date. The action of these compounds in stimulating the bone marrow probably simulates a normal physiologic mechanism. Sabin^{9, 10} showed the presence of nonmotile polymorphonuclear neutrophils in normal living blood. This suggested to Doan⁸ the hypothesis that the disintegration products of these cells, one of which is nucleic acid, supplied the stimulus to the bone marrow for the production of new cells. As is well known, clinical application of this theory has been found in agranulocytic angina, where favorable clinical and hematologic results ensue when pentose nucleotide K96 is given intravenously.¹¹ Reznikoff¹² published the first report on this subject in 1928.

The injection of leucocytes, one of the most important constituents of which is nucleic acid, to stimulate bodily resistance, began with Hiss in 1908.¹³ He used rabbit leucocytes obtained by pleural injection of aleuronot. After twenty-four hours 30 to 60 c.c. of turbid fluid was obtained. This was centrifuged, the cells washed in saline, and emulsified in distilled water. Both supernatant fluid and cell residue were used separately and together. Hiss concluded that these extracts had a distinct modifying and curative action when given subcutaneously and intraperitoneally to rabbits and guinea pigs. His results in human epidemic meningitis¹⁴ and lobar pneumonia¹⁵ led him to conclude that he was dealing with "an agent which further clinical test would not unlikely prove of definite therapeutic value."

Subsequently very little was done with leucocytic concentrate until Strumia in 1934¹⁶ claimed to demonstrate that intramuscular injections of this material from human donors into patients with severe neutropenia were followed in most cases by an increase of mature granulocytic cells in the circulation, together with clinical improvement. In three normal people treated and studied in this way, none showed an increase of granulocytes or young forms above the normal physiologic fluctuations. Following Strumia's method, Davidson and Shapiro¹⁷ used human leucocyte concentrate in one case of neutropenia which followed the use of dinitrophenol.

Another method of leucocyte administration is by whole blood transfusion. It is agreed by all that transfusion stimulates the blood-forming functions. This effect may in large part be due to the disintegration of the injected leucocytes. Transfusions are being used by us in atrophic (rheumatoid) arthritis with definite beneficial but certainly not curative effect.

We decided to use leucocyte concentrate in atrophic (rheumatoid) arthritis because of the nucleic acid content of these cells, and because it was thought that normal leucocytes might contain a hormone lacking in patients with atrophic (rheumatoid) arthritis.

PREPARATION OF LEUCOCYTE CONCENTRATE

The leucocyte concentrate was prepared in the following manner. A healthy donor was selected and the presence of venereal and other active infection was eliminated. Three hundred cubic centimeters of blood were aspirated by venipuncture into sterile bottles containing 50 c.c. of physiologic saline and 20 c.c. of 10 per cent sodium citrate. This material was centrifuged for one hour at 2,600 revolutions per minute in tubes one inch wide by six inches long. After removing the serum, the supernatant leucocyte layer was drawn off in sterile Pasteur bulbs. This material was pooled, again centrifuged in the same manner, and the supernatant leucocyte layer was drawn off and placed in rubber-capped vaccine vials. From 300 c.c. of whole blood the yield of leucocytes, partially mixed with red blood cells, was from 25 to 30 c.c. Forty-eight-hour sterility tests were made.

This material was kept on ice and 3 to 6 c.c. was administered to each patient intragluteally, in some cases three days a week, in some seven days a week. The treatment was kept up from three weeks in one case to nine months in the case longest under observation. The local reaction about the site of the injection was negligible. There were no evidences of general reaction except in one instance, where it was subsequently found that the leucocyte concentrate was contaminated.

METHOD OF ADMINISTRATION

Ten patients with atrophic (rheumatoid) arthritis were selected by the usual criteria. Their condition ranged in severity from marked generalized, crippling deformity in a child ten years of age, to mild but definite arthritis in elderly subjects. A summary of one case will give an idea of the procedure used.

CASE 1.—(No. A95348.) Female, aged twenty-eight. Diagnosis: atrophic (rheumatoid) arthritis. Symmetrical, generalized periarticular swelling with marked limitation of motion and pain on motion of hands, wrists, elbows, shoulders, and knees. Agglutination reaction for *Streptococcus hemolyticus* AB₁₃ and NY₅ positive to dilution 1-320. Initial sedimentation rate 49 mm. per hour. The blood count was as follows: red blood cells 3,460,000, hemoglobin 68 per cent, white blood cells 9,300, polymorphonuclear neutrophils 64 per cent, mononuclears 4 per cent, lymphocytes 32 per cent.

On Sept. 13, 1934, 1 c.c. of leucocyte concentrate was administered intragluteally, and rapidly increased by almost daily injections to 3 c.c. and thereafter varied from 3 to 6 c.c.

In four weeks there was marked improvement in the patient's condition. She was decidedly stronger, had less pain, and almost unlimited motion of the upper extremities. She resumed her household duties for the first time in a year. She discontinued the use of aspirin, whereas formerly she had taken up to 45 gr. a day. She noted a decrease of pallor in her skin, especially her hands.

After the first month progress was less marked. Once she had urticaria for one week. Improvement has been irregular but continuous, so that on the last examination on May 17, 1935, she had unlimited motion and was free from pain except in her knees. Up to this date she had received 412 c.c. of leucocyte concentrate.

During treatment blood counts were repeated. There was no change either in the leucocyte or in the erythrocyte count. The sedimentation rate fluctuated from 24 to 49 mm. an hour, the last test on April 30, 1935, being 40 mm.

The other nine patients were similarly treated, although the duration of treatment was less. A summary of the therapeutic results in these cases is given below. It is important to point out that although one of the theoretical reasons for the administration of the leucocyte concentrate was to stimulate the bone marrow, in no case was a change in the leucocytes observed above that attributable to the normal physiologic fluctuations. In one case where many counts were made throughout two days, the same results were obtained.

SUMMARY OF RESULTS

Ten cases of atrophic (rheumatoid) arthritis have been treated with leucocyte concentrate. No case can be considered cured. Six patients show decided symptomatic and general constitutional improvement. In the remaining four patients improvement was only slight or questionable. Improvement consisted of a decrease in pain, an increase in joint motion, and a feeling of increased strength and well-being. These changes were not, however, accompanied by improvement in the blood picture or in the sedimentation rate.

DISCUSSION

It is clear to us that intragluteal injections of leucocyte concentrate have a definite beneficial effect in some cases of atrophic (rheumatoid) arthritis. The effect is apparently in no way specific. In view of the lack of change in the sedimentation rate, it appears that its effect is constitutional and only indirectly affects the arthritis. Its mode of action is obscure. The amount of nucleic acid present in the injected leucocytes is not sufficient to affect the blood picture. The beneficial effect may be purely a nonspecific protein reaction but the effect was obtained more quickly, was more lasting, and in every way far superior to that obtained by any foreign protein so far used by us.

An attempt was made to use animal leucocytes. Fresh sheep and horse blood was obtained and the leucocytes were centrifuged off in the way described above. The local and general reactions were so severe, however, that this method had to be abandoned.

CONCLUSIONS

1. The intragluteal injection of whole human leucocytes into patients with atrophic (rheumatoid) arthritis is followed in some cases by prompt improvement in the joint symptoms and in the general well-being of the patient.
2. In no instance was the patient considered cured.
3. The injections of leucocyte concentrate did not change the total circulating leucocytes, or their relative proportions, beyond the usual physiologic fluctuations. In no case was the sedimentation rate significantly or permanently changed.

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THE USE OF CINCHOPHEN IN THE TREATMENT OF CHRONIC ARTHRITIS

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INTRODUCTION.—Arthritis is the most disabling and costly of all the chronic diseases. It was known to the ancients and numerous remedies for its relief have been advocated down through the ages. Its incidence today is of no less importance than that of a generation ago. It is estimated that in this country arthritis is more prevalent than tuberculosis and heart disease combined.

During the past fifteen years rapid advances have been made in our methods of treating this malady. This is to a large extent the result of a better understanding of its classification and of the various etiologic factors that tend toward the persistence of the disease. Since no single etiologic factor has been discovered as the sole cause of any of the various types of arthritis, it naturally follows that we must utilize to the fullest extent every efficient method we have at our disposal for combating its onset and progress. While not in any way wishing to detract from the credit which should be given to such well-known methods of treatment as rest, dietary measures, removal of foci of infection, physiotherapy, posture, climate, etc., the authors feel that the drug treatment of arthritis during recent times has not received the proper degree of attention which it justly deserves. It would appear that perhaps this may be due to four factors. (1) The dosages employed in most instances have not been large enough to secure the desired therapeutic result because most physicians use minimal doses, whereas the method of choice is to increase the dose gradually up to the point of intolerance. (2) In many instances the use of medication has not been persisted in for a sufficient length of time. (3) The prevailing impression of the medical profession is that the relief seems to be due entirely to the analgesic effect and they have entirely neglected to take into consideration the beneficial effects on the kidney and the liver in stimulating increased elimination of nitrogenous waste products. Finally, (4) Cinchophen, our most important drug, has been too hastily condemned by many physicians because of reports in the literature which seem to indicate that this drug and its derivatives are toxic to the liver and kidney, because many deaths from acute yellow atrophy have been attributed to its use. In spite of this increasing apprehension the authors of this paper have continued to use cinchophen routinely in all cases of chronic arthritis over a period of ten years, about 1,800 cases in private practice and 760 in hospital clinics, and have never seen a single case of jaundice from its use during that time. During the past three or four years the authors have met several prominent physicians who have stated that they had given up the use of cinchophen entirely on account of the alleged toxic effect upon the liver. In one hospital an order was sent forth prohibiting any

physician in the institution from prescribing cinchophen. Many other physicians refuse to administer this drug for fear that they may later become involved, from a medicolegal aspect, in case the patient should develop jaundice from any cause. The authors do not contend that cinchophen is an entirely harmless drug, but they feel that the reports of liver damage have been grossly exaggerated and that a careful analysis of these reports would prove valuable in an effort to clear up the conflicting views on the subject.

SHORT HISTORY OF DRUG THERAPY IN ARTHRITIS

Brunton's *Therapeutics and Materia Medica* of fifty years ago set forth the merits of over a hundred remedies for the treatment of rheumatism. Foremost among these were colchicum, sodium salicylate, and potassium iodide. Since benefits were attributed to so many different drugs, it was obvious that there was no one which was really effective in all cases. Colchicum, a natural product, for example, in sufficient doses relieved the pain in gout promptly and satisfactorily but caused marked gastric irritation, weakness, and diarrhea. Salicylates (originally obtained from oil of wintergreen although later synthesized) sometimes produced not only irritating effects on the stomach but had the distinct disadvantage of producing renal damage when doses large enough to be effective were employed.

An attempt was made by various investigators to obtain a satisfactory compound which would adequately relieve pain and at the same time not upset the gastrointestinal tract. Cinchophen obviously met these requirements.

History of Cinchophen Therapy.—Nicholaier and Dohrn¹ in 1908 called attention to the fact that this product was an excellent analgesic and antipyretic in rheumatic conditions. They believed that it definitely increased the excretion of the end-products of protein metabolism, more especially uric acid and uræa.

Davis² confirmed the fact that it was an excellent analgesic, etc., and also stated that it diminishes congestion of the joints.

Fine and Chace³ believed that the beneficial effects these patients had were due to the increased permeability of the kidney.

Folin and Lyman⁴ demonstrated that the increased uric acid in the urine following the administration of cinchophen was represented by the amount of this substance that had previously accumulated in the blood stream due to the associated kidney insufficiency.

McLester⁵ stated that the use of cinchophen diminished the amount of uric acid in the blood 50 per cent and increased the output of uric acid in the urine 300 per cent.

Nicholaier and Dohrn¹ pointed out that the output of uric acid is greatest in the first thirty-six hours after administration and following this period, and remains at the normal level for the duration of the use of the drug. However, they pointed out, if it were discontinued for a few days and then started again, they were able to reproduce an increase in the output of uric acid.

During recent years considerable attention has been devoted to the effect of cinchophen upon the liver. Brugsch and Horsters⁶ found that sodium

cinchophen given in doses of from 0.8 to 3 gm. increased the secretion of bile from 8 to 864 per cent. The total quantity of solids, acids, viscosity and surface tension quotients and pigments of twenty-four-hour collections were all increased.

Grunenberg and Ullman⁷ reported increase in bile in the duodenal contents following the administration of cinchophen to healthy individuals as well as patients suffering from catarrhal jaundice. Brugsch⁸ reported favorable results following the use of cinchophen in treating jaundice and subacute atrophy of the liver. Lichtman⁹ confirmed this statement and showed that single or even repeated doses of 0.45 gm. of cinchophen are not toxic, even in the presence of severe damage to the liver. Mendel¹⁰ observed what Davis² later confirmed, that the use of cinchophen diminishes congestion in and around inflamed joints. He believed that this is probably due to the paralyzing effect of cinchophen on the ameboid movement of the leucocytes. He argued that the increased amount of protein thrown into the blood stream is the result of the destruction of the leucocytes and is sufficient to explain the increased excretion of uric acid following the use of this drug.

Reports of Toxic Action of Cinchophen.—In 1913 Phillips¹¹ first described skin reactions to cinchophen. This report was followed by similar ones from Schroeder,¹² Worster-Drought,¹³ Reichle,¹⁴ Cabot,¹⁵ Parsons and Harding,¹⁶ and Rabinowitz.¹⁷ These observers felt that it was a dangerous drug to use; that many people had an idiosyncrasy to it and that even small doses might initiate an attack of jaundice which occasionally proved fatal.

In October, 1932, J. S. Davis, Jr.,² compiled an excellent review of all the literature on the subject and also at the same time published the results obtained in a series of 200 consecutive cases in which the patients had been taking cinchophen and neocinchophen. No fatal results were observed. Thirty patients, however, had some toxic symptoms. None of these were of a serious nature, and none of the patients were confined to bed because of symptoms.

In 1931 E. P. C. White¹⁸ made a careful study of twenty-one selected cases of advanced arthritis. All the patients took two capsules of Mono-iodo-cinchophen three times daily for periods ranging from seventeen to twenty-four weeks. She emphasized that, while there have been a number of deaths attributed to the use of cinchophen, there is a relatively small number of proved cases in proportion to the amount of cinchophen and its derivatives consumed in the United States, which was approximately 90,000 pounds a year. She pointed out that the symptoms of toxicity and their severity are not in proportion to the length of time the drug has been taken, nor to the amount of the drug ingested. At no time during the observation period did the extensive laboratory studies made of these twenty-one patients show any variation from the normal. Eaton¹⁹ also confirms these observations. He has treated several thousand cases in the Arthritis Clinics of the Flower and Metropolitan Hospitals of New York, and has never seen a case of jaundice following the administration of cinchophen. He has recently given 6,000 intravenous injections of 7½ gr. of cinchophen combined with 34 per cent hexamethylenetetramine, together with the oral administration of cinchophen in these cases, without any deleterious

rious results. Fine and Chace³ felt that cinchophen and neocinchophen were the drugs of choice when for any reason it seemed desirable to favor the kidneys.

Reports on Animal Experimentation with Cinchophen.—Barbour and Lozinsky²⁰ of McGill University have demonstrated by animal experimentation the relative toxicity of cinchophen and its derivatives. The results of their experiments showed that aspirin in dogs is more than twice as toxic as cinchophen, when given by mouth. A careful review of the literature to date fails to reveal any authentic reports of liver damage in experimental animals.

Reported Cases of Cinchophen Poisoning.—It would seem well worth while at this point to attempt a critical review of the reported cases of cinchophen poisoning and to cite our own clinical experience which covers some 2,560 cases over a period of ten years in an effort to counteract the apprehension now so prevalent in the medical profession with regard to the use of cinchophen. Between the years 1913 and 1933 the literature reveals a total of 131 cases of cinchophen poisoning, 96 of which can be immediately excluded, 48 of these cases because of fragmentary data and the other 48 cases because there were no autopsies or operative proof to confirm the diagnoses. In the 96 cases of this series which we exclude there were 30 that showed as their toxic symptoms only urticaria. Such cases should not be considered in the same category as those which developed jaundice, acute yellow atrophy, or even those in which death occurred following the alleged use of cinchophen. The authors do not deny that in rare instances skin reactions do occur coincident with the use of cinchophen, but they have also seen it occur with equal frequency after the use of other drugs, vaccines, and occasionally after colonic irrigations. In our cases, since we use all of these methods of treatment in almost every case, we never could be sure that the urticarial lesion was due solely to the use of cinchophen. The urticarial reaction is unpleasant, but it is not dangerous and does not interfere in any way with the successful outcome of the case. It can usually be controlled by the elimination of the drug and the use of adrenalin and/or sodium thiosulphate. Of the remaining 66 cases, it is obvious that the diagnosis, even in the hands of expert clinicians, was so uncertain that no definite conclusions could justly be drawn as to the cause of their jaundice. Consequently, it would be most unfair to consider these cases in any critical review of the reported cases of liver damage alleged to cinchophen.

The 35 remaining cases came to postmortem. Ten of these obviously had other causes of death, viz.: 2 followed operative procedures and 8 had a typical cirrhosis of the liver. In the remaining 25, death was attributed to acute yellow atrophy of the liver. A careful study of these cases, however, reveals that in 7 cases other etiologic factors which in themselves could account for the pathologic changes were found in the liver, viz.: (1) abscesses of liver and lungs; (2) previous history of eclampsia; (3) history of recurrent severe attacks of typhoid fever; (4) Wassermann 4-plus; (5) history of having received 25 c.c. antipneumococcic serum followed by a severe serum reaction; (6) inoperable cancer of the cervix; and (7) pituitary tumor. Thus, out of all reported cases of cinchophen poisoning in the literature (131) through 1933, in only eighteen (13 per cent) did the pathologic findings support such a clinical diag-

nosis. The proof that cinchophen did cause death in these instances hinges upon the single fact that the patients developed acute yellow atrophy coincident with the administration of the drug. It seems to the authors that the critics of this drug have assumed a great responsibility in claiming that this is *prima facie* evidence of guilt on the part of the drug employed because they (the critics) are faced with the undeniable fact that acute yellow atrophy occurred long before cinchophen was ever utilized therapeutically. Moreover, acute yellow atrophy occurs with relative frequency and may occur in patients with arthritis who have never had cinchophen. It cannot be denied that, when it does occur in arthritis, the onset of acute yellow atrophy may merely be a coincidence.

In the state of New York alone in the years from 1923 to 1933 there were 712 deaths from acute yellow atrophy in 7,174,572 hospital admissions. The authors take the liberty to assume, after comparing the above figures, that if all cinchophen administration were stopped immediately, acute yellow atrophy would still go on in the general population at the same rate.

Chance Toxic Dose.—In the eight-year period from 1924 to 1932 inclusive, there were about 660,000 pounds of cinchophen produced and consumed, representing approximately 660 million doses of $7\frac{1}{2}$ gr. each. Despite this, during this period there were only 38 reported deaths in the United States attributed to the use of this drug, making the chance toxic dose 1:17,000,000, which is as low as one could reasonably expect for any active therapeutic agent. Cinchophen is not a harmless drug, but it is a very effective one and when used with proper care and reasonable precautions, its benefits far outweigh its limitations. In reply to a recent query the *Journal of the American Medical Association* stated that, "When he gives it with proper precautions, the physician carries no more liability in the prescribing of this than he does of any other potent agent." Salicylates and cinchophen can safely be administered in very large doses and represent a fortunate combination of both antipyretic and analgesic qualities which make them more suitable, convenient and desirable than the employment of two or more drugs possessing the same actions individually.

Report of Personal Experience with the use of Cinchophen.—The authors have been using cinchophen almost routinely in private practice and in the Arthritic Clinics of the Hospital for Ruptured and Crippled of New York, and the Roosevelt Hospital of New York, during the past ten years. Not only have no deaths occurred but they have seen only one mild case of catarrhal jaundice and have never seen a case of severe jaundice or of acute yellow atrophy following the use of cinchophen. It must be admitted that they have only seen an occasional attack of urticaria. These are seldom serious as they last only a few days and are easily controlled by stopping the drug. In obstinate cases the attack can usually be quickly terminated by the use of hypodermic injections of adrenalin with or without the intravenous use of sodium thiosulphate. In many of these cases the urticaria definitely was proved to be due to some other etiologic factor. The authors have used cinchophen combined with urotropin intravenously in a series of fifty cases and have not noted any deleterious or toxic effects.

Our Method of Administration.—The authors usually start the use of cinchophen with doses of $7\frac{1}{2}$ gr. three times daily, but it is important to emphasize that in the beginning of the treatment they insist upon seeing the patients three times a week so that any case of gastric irritation, nausea, or itching may be noted as soon as it develops and all medication discontinued. They have frequently found that at a later date they can start with a smaller dose and continue to administer the drug safely. The patient is not allowed to know what drug he is taking. This control is rigidly enforced as the authors do not believe that cinchophen is a safe drug to be sold over the counter, and feel that probably most of the reported toxic effects of cinchophen have been due to self-medication.

If the use of three tablets of $7\frac{1}{2}$ gr. each a day is not sufficient, the dose is increased to four a day; but the authors find that this is about the largest dose that can safely be taken by patients over a long period of time. In case the pain is not relieved the medication is reinforced by adding 5 gr. of aspirin three times a day. An additional factor of safety is the fact that a great many of the patients have had colonic irrigations during the time they have been taking the cinchophen. Control of the gastrointestinal tract of the patient tends to facilitate the use of cinchophen in patients who do exhibit signs of gastric irritation from the drug by proper dietary measures and the use of colonic irrigations.

Neocinchophen is generally believed to be less dangerous to use than cinchophen, but larger doses are required to obtain the same degree of clinical improvement. The increased doses of neocinchophen produce the same gastrointestinal and urticarial disturbances which occasionally result from the use of cinchophen. The patients object to ingesting the larger doses of neocinchophen and to the greater cost of this drug. In practice, therefore, cinchophen is the more desirable drug to use.

SUMMARY

The history of cinchophen is reviewed. The action of the drug, its usefulness in the treatment of arthritis and in liver diseases is discussed. The toxic actions of cinchophen which are reported in the literature are reviewed. Of 131 cases of cinchophen poisoning reported in the literature between the years 1913 and 1933 only 18 had pathologic findings to support a clinical diagnosis of liver damage following the use of cinchophen. In a critical review of the literature covering these twenty years the authors found that there were only 18 deaths, and that approximately 90 million doses of cinchophen were consumed during this time. They therefore feel that the chance toxic dose is too small to preclude the use of this medication. In 2,500 cases treated by the authors with the oral administration of cinchophen and 50 cases treated by intravenous injection of cinchophen there has been no evidence of liver damage. The authors believe this is due largely to the rigid control they exercise over the use of the drug and to the fact that they see their patients every third day for the first two weeks of its administration. It has been emphasized that they never give over 30 gr. a day. At the same time the importance of keeping the gastrointestinal tract in good condition

has been stressed. A review of the literature shows that one group of clinicians believe that the use of cinchophen is dangerous, and give as their reasons its toxic action on the liver, while an equally well-qualified group of clinicians maintain that they use cinchophen, both here and abroad, for its stimulating effect on the liver in cases of catarrhal or even severe jaundice. The experience of the authors in 2,500 cases would seem to favor the latter view, and would seem to indicate that the fatal cases of acute yellow atrophy were either coincidences, or in some way were due to lack of control in the administration of the drug. The authors therefore believe that the use of cinchophen is justified and carries with it no more danger or responsibility than the use of any other potent pharmaceutical preparation.

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DISCUSSION

DR. HOMER F. SWIFT, NEW YORK CITY.—The report of Dr. Snyder represents a type of investigation that is much needed in the application of drugs in the treatment of patients with disease. Natural idiosyncrasy or acquired hypersensitiveness not infrequently makes it impossible to give many drugs in therapeutic doses. Indeed, some individuals are so sensitive to some drugs that a minimal dose will elicit alarming, even fatal, phenomena. The ratio of toxic to therapeutic dose is quite variable in different subjects; and this makes careful study of each case most important. These more or less self-evident facts are sometimes forgotten in the enthusiasm of the moment to record the alarming by-effects of drugs. While it is important to be familiar with these unfavorable effects it is equally desirable to know how frequently they occur. The data presented by the authors seem to indicate that the serious sequelae from cinchophen are relatively uncommon. But that they do occur we can be quite certain, both from a perusal of the literature and from personal experience. Fortunately we have several chemically unrelated drugs which seem to have comparable action on the symptoms of rheumatism, so that when a patient is encountered who reacts unfavorably to one, we are in a position to switch to another. The relative cost of the different remedies is an item worthy of consideration when prolonged medication is anticipated. Our final decision will be influenced by the consideration of all of these factors.

THE NATURE OF RHEUMATIC FEVER*

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IN BEGINNING this symposium it would be well to define the nature of the disease under discussion. This will be attempted so far as contemporary knowledge permits, for it should be recognized that until the etiology is conclusively demonstrated, and specific diagnostic measures are available, most discussions must, of necessity, consist in reviewing theories that knit together current observations.

CLINICAL CHARACTERISTICS

The clinical manifestations of a disease often give a clue concerning its nature, particularly when a given pattern is followed closely enough to permit clear differentiation from not too distantly related conditions. This, upon first glance, would seem to apply to rheumatic fever, and especially to that type formerly known as acute articular rheumatism, with migratory polyarthritis, pyrexia, toxemia, and cardiac symptoms as prominent features. Many variations from this, so-called, typical picture exist; in fact they are sufficiently numerous apparently to comprise the majority of cases encountered in a large general clinic where both children and adults are treated. Monosymptomatic manifestations, such as cardiac insufficiency or chorea may predominate, and the accompanying signs of mild infection, with undernutrition, slight fever, low grade leucocytosis, accelerated erythrocyte sedimentation rate and altered electrocardiograms, may require careful documenting before the rheumatic nature of the disturbance can be determined. In fact, the symptomatology may be so obscure that the pathologist's verdict, derived from microscopic examinations, must be the deciding factor.

Temporal variations are equally outstanding. On the one hand, we may see polyarthritis, fever, and toxicity of short duration; the patient recovers and is apparently free from any further rheumatism for the remainder of his life. On the other hand, one encounters a patient with low grade fever, progressive carditis, occasional congestive failure, continued slight leucocytosis, and increased erythrocyte sedimentation rate lasting for years, until finally acute cardiac failure drops the curtain on a life of chronic invalidism. Again, persistent arthritis may be so marked that the physician is in doubt as to whether he is dealing with a case of acute arthritis deformans or of subacute rheumatic fever. First attacks of chorea may be typical, while subsequent recurrences are not infrequently manifestations of habit spasms. Subcutaneous rheumatic nodules are sometimes the chief signs in a person who considers himself to be in perfect health; and

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how frequently does the cardiologist encounter full-blown mitral stenosis in patients who deny previous rheumatic manifestations, or does the pathologist find Aschoff bodies in the heart of a subject whose clinical history is likewise free from rheumatic stigmas? A realization of the foregoing possibilities makes the experienced clinician cautious when facing a combination of symptoms that have many of the characteristics of rheumatism and yet may possibly be induced by other infections.

One should also recall the tendency for manifestations to recur, especially during childhood, while after puberty this tendency decreases. Puberty, indeed, seems to constitute an important and critical stage in the life of the rheumatic youth. If, because of previous damage, his heart has undergone marked hypertrophy and is unable to meet the demands of rapid bodily growth, ensuing failure soon terminates the picture. If, on the other hand, the child has sufficient reserve to pass this critical period, he will probably live through succeeding years with distinctly fewer rheumatic relapses than he suffered before the age of puberty. The possible relationship between immunity, or resistance, to rheumatism and the action of sex hormones is worthy of more careful study. In passing, one might mention the apparent connection between certain phases of the menstrual cycle and the appearance of rheumatic relapses seen in some women; it occasionally is observed over periods of many months.

The question of the nature of rheumatic relapses is, as yet, unanswered. Are they the result of introduction of fresh infectious material into a susceptible subject, such as we see in erysipelas; are they due to an altered reactivity of tissues so conditioned that slight insults of various types lead to a peculiar mode of response; or are they manifestations of prolonged residence of some infectious agent in the rheumatic subject with periods of almost complete immunity followed by episodes of diminished resistance, comparable to the relapses one sees in syphilis or malaria? Even in patients who appear to be having a continued infection one encounters phenomena indicating alternate cycles of attempts at recovery followed by periods of lowered resistance.

NATURE OF THE HISTOPATHOLOGIC CHANGES

The two active inflammatory responses to injury, viz., exudation and proliferation, are prominent features of the rheumatic processes. The former is illustrated in and about an acutely swollen joint, the latter in the subcutaneous nodule, or in the myocardial Aschoff body. While exudative and proliferative are convenient descriptive terms to apply to different pathologic pictures, they do not represent mutually exclusive processes, and proliferation often exists in the presence of a rheumatic exudate. Both are responses to injury: the exudate, consisting of plasma, or of synovial fluid and wandering cells, is apparently earlier and more evanescent; the proliferate appears later and is more lasting.

McEwen's¹ studies indicate that the proliferated cells are distinctly different from the epithelioid cells encountered in tuberculosis or from those in syphilitic lesions. They are apparently nonphagocytic, and are probably very primi-

tive forms arising from resting mesenchymal cells; although it is possible that at times they may derive from endothelial elements. Their peculiar architectural arrangement in the form of submiliary nodules is claimed by many pathologists to be specific for this disease; other observers regard their presence merely as evidence of a response to injury; and these two schools of thought apparently cannot be reconciled. The Aschoff body, when fully developed, may present a highly characteristic picture; but often cellular arrangements are such that their true character is not apparent unless compared with the, so-called, specific granuloma.

Possibly even more important for an understanding of the pathogenesis of this disease is the altered intercellular mesenchymal ground substance. The collagen fibers show evidence of injury, varying from simple focal edema to fibrinoid swelling and focal necrosis. According to Klinge² this precedes proliferation of the primitive cells; indeed, he thinks that this proliferation is the direct response to alterations in the mesenchymal ground substance. What induces these changes is a matter of conjecture; and were it definitely known we possibly might be much closer to a definite understanding of the etiology of this disease. Klinge thinks that it is a manifestation of tissue hyperergy, for he could easily demonstrate fibrinoid swelling in the tissues of rabbits repeatedly injected with foreign protein; and possibly upon this basis one could postulate that the injurious substance was formed by a union of antibody and antigen, presumably of bacterial origin. Fibrinoid swelling, on the other hand, can be induced by bacteria or bacterial toxins, and has also been described in the tissues of noninfected scorbutic animals.^{3, 4} Its occurrence, therefore, cannot be definitely attributed to any one type of noxious agent. So far as we know, it has not been induced by filtrable viruses. According to Rivers,⁵ all viruses apparently attack primarily either the nucleus or cytoplasm of cells, and the inflammatory reaction is secondary to this cellular injury. We cannot regard the ground substance as cytoplasmic in nature, but rather as an excretory product of the mesenchymal cells; it has more of a supporting than an active metabolic function. If we are correct in assuming that filtrable viruses attack only the active cell bodies or nuclei, it would appear that some other factor was responsible for the focal injury so characteristic of the rheumatic process. On the other hand, there may be primary points of attack by viruses as yet unrecognized, and if this should be the case, rheumatic fever might be included in this new category.*

STREPTOCOCCI AND RHEUMATIC FEVER

That streptococci may play an important rôle in the causation of rheumatic fever has been the subject of discussion for many years, and recently the possible relationship of hemolytic streptococci has been specially stressed. To

*Andrewes has recently described a variant of the rabbit fibroma virus of Shope, which variant induces chiefly inflammatory lesions in rabbits. The evolution of these virus-induced inflammatory lesions has not been minutely described; but Andrewes' observations apparently afford an exception to the general rule laid down by Rivers that invasion and injury of cells by virus precedes inflammation. (Andrewes, C. H.: Viruses in Relation to the Aetiology of Tumours, *Lancet* 2: 63 and 117, 1934; Faulkner, G. H., and Andrewes, C. H.: Propagation of a Strain of Rabbit Fibroma Virus in Tissue-Culture, *Brit. J. Exper. Path.* 16: 271, 1935.)

review this subject completely would be too time-consuming; hence only the more salient points will be discussed. The long recorded relationship between prodromal tonsillitis or severe nasopharyngitis and rheumatic fever is a matter of common experience. This is especially obvious in adults suffering from their first attack or in those free from the disease for long periods. Following the initial upper respiratory infection there is an apparent quiescent period of a few days to four weeks, the so-called latent period, before the characteristic rheumatic syndrome appears. Unfortunately, careful study of patients during this period is usually impracticable; and in most instances, where carried out, the subjects have been youthful patients in convalescent homes, who have only recently recovered from an attack of rheumatism. Coburn and Pauli^{6, 7, 8} have studied nurses, some previously rheumatic and some not. Because tonsillitis is usually associated with heavy hemolytic streptococcal infection, and also because severe nasopharyngitis is often similarly characterized, it has been quite generally assumed that the rheumatic sequelae to these respiratory infections have had these microorganisms as the immediate causative agents. Several observers have shown that precipitins⁸ against certain chemical fractions of hemolytic streptococci and also that antistreptolysins^{9, 10} and antistreptofibrinolysins¹¹ appear in the blood about the time of onset of rheumatic symptoms. It has, therefore, been tacitly, if not actively, assumed that some of these antibodies may possibly play a pathogenic rôle in this disease; such an argument is particularly cogent if it is postulated that the pathogenesis rests in part on an allergic basis. Todd⁹ originally demonstrated that a large proportion of patients with active rheumatic fever have, what he considered, abnormal concentrations of antistreptolysins in their serums, and therefore concluded that this was highly suggestive evidence of recent hemolytic streptococcal infection. Coburn and Pauli⁸ concurred with these conclusions, but reported that the appearance of precipitins against streptococcal proteins was more characteristic of active rheumatic infection than was the occurrence of antistreptolysins.* Most observers agree that high antistreptolysin titers are characteristic of hemolytic streptococcal infections rather than of rheumatic fever. Our own experience,¹² as well as that of others, indicates that precipitins against streptococcal proteins are usually demonstrable following streptococcal infections unaccompanied by rheumatism. We are, therefore, forced to the conclusion that the presence of all antistreptococcal antibodies thus far described is characteristic of hemolytic streptococcal infection rather than of the rheumatic state, and that none of these antibodies are peculiar, either qualitatively or quantitatively, to this rheumatic state.

Wilson and her coworkers^{13, 14, 15} have, indeed, recently concluded that their data, dealing with the isolation of hemolytic streptococci from the throats of rheumatic and nonrheumatic children and with the occurrence of antistreptolysins in their serums, indicate no relationship at all between streptococcal

*Subsequent to the preparation of the present review Coburn and Pauli (Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. II. Observations on an Epidemic of Influenza followed by Hemolytic Streptococcus Infection in a Rheumatic Colony, *J. Exper. Med.* 62: 137, 1935) recorded an outbreak of rheumatic relapses in a group of rheumatic girls in whom the symptoms and antistreptolysin curves ran closely parallel.

infections and rheumatic fever. Data so apparently out of accord with the experience of most other investigators merit some comment, because neglect of prophylactic precautions based upon a streptococcal theory of etiology (at least contributory) may lead to serious consequences for rheumatic patients. Admitting that hemolytic streptococci were recovered from the throats of most of their patients, one would like to know the kind of streptococci. What were the colonial, pathogenic, or toxicogenic characters of the streptococci recovered? To what serologic group^{16, 17} did they belong? So far as we now know members of Group A and possibly of Group F comprise the majority of strains probably pathogenic for man. There is reason to believe that human beings often carry members of other groups in their throats with impunity; and, in fact, according to the findings of Lancefield and Hare,¹⁷ strains not belonging to Group A can live in such highly vulnerable areas as the birth canals of parturient women without inducing disease. Furthermore, these non-Group A strains do not induce antistreptolysins against the soluble hemolysins produced in broth by Group A streptococci.¹⁸ If then, for sake of illustration, a patient were carrying Group B strains in his throat this would have no influence on the antistreptolysin content of his serum when tested by the usual methods. As carried out by these investigators, the identification of hemolytic streptococci by simple inspection of growths of mixed cultures on blood agar plates is exceedingly difficult; and obviously this technic gives no idea of the serologic group to which the streptococci belonged. Granting, however, that the cocci recovered were all members of Group A, this is no assurance that they would induce a rise in the antistreptolysin curve in the carrier's serum, for in our experience roughly 20 per cent of patients definitely infected with proved Group A streptococci failed to show a significant rise in the antistreptolysin in their serums. The carrying of pathogenic streptococci deep in the tonsillar crypts or in the lymphatic glands might escape detection in cultures made from pharyngeal swabbings; but such deeply situated streptococci might easily induce the formation of antistreptolysins in high titers and still the causal relationship be unobservable. Finally, the failure of Wilson's group of children to show the usual seasonal late winter and early spring rise in rheumatic relapses is different from the experience of most observers in New York City. This unusual happening suggests that possibly some prophylactic measures or other factors may have interfered with the customary course of events. It explains, in part, how difficult it is to compare these observations with those of others.

Coburn and Pauli's data and conclusions^{6, 7, 8} are the direct antithesis of those just discussed. These observers carefully investigated the streptococci isolated, and identified at least six different types belonging to Group A. Dr. Lancefield has proved the existence of at least ten different serologic types belonging to Group A among the strains isolated from our rheumatic patients; and in Griffith's¹⁹ recent paper fifteen different types from rheumatic individuals were recorded as identified by the slide agglutination technic. As in all of the works just cited the same types were recovered from nonrheumatic patients with streptococcal infections, it seems obvious that none of these strains carry any unique rheumatism-inducing properties.

Coburn and Pauli's⁶ numerical data are worthy of citation. During a three-year period, in one-third of their rheumatic subjects there were neither hemolytic streptococcal infections nor rheumatic recrudescences, while in another third the order of events was characterized by an appearance of streptococci in the throat prior to a rheumatic attack. Among the remaining third, one-sixth had relapses unpreceded by hemolytic streptococcal infections, one-fourth had many hemolytic streptococci in the throat without a return of rheumatism, and in the remainder no definite relationship between the two phenomena could be demonstrated. These data, which indicate that although the relationship between streptococcal infection and rheumatism is highly suggestive of having a causal character, it is not by any means absolute.* †

Schlesinger, Signy and Payne²⁰ could demonstrate precipitins against certain chemical fractions of hemolytic streptococci in only one-half of their rheumatic children. These authors state that when these antibodies were present they appeared to be related to a complicating streptococcal infection rather than to the rheumatic syndrome, for many patients with typical rheumatic symptoms, but without a recent history of streptococcal infection, failed to develop precipitins. Our own studies¹² of antibodies in the serums of patients taken repeatedly during the course of an attack have failed to show any constant relationship between severity of symptoms and the presence of precipitins against either the "C" (carbohydrate) or "P" (nucleoprotein) fractions of Group A hemolytic streptococci. In this connection, however, it should be mentioned that in animals, at least, there is not necessarily a direct connection between a hyperergic state of their tissues and the presence of antibacterial antibodies in their serums.²¹

RHEUMATIC FEVER AND AN ALLERGIC STATE

Much attention has been paid in recent years to the relationship between allergy (better hyperergy), and rheumatic fever. Because the tests have been largely made with the products of streptococci, thought to have some causative relationship to the disease, we shall confine our discussion largely to this phase of the subject. Rheumatic patients have a marked degree of hypersensitiveness to streptococcal proteins or vaccines when introduced either intracutaneously

*These authors have very recently stated that although there is strong evidence indicating the importance of infection with hemolytic streptococcus in initiating rheumatic activity, it is their opinion that this is not the only factor underlying the development of the rheumatic state. (Studies on the Immune Response of the Rheumatic Subject and Its Relationship to the Activity of The Rheumatic Process. III. Observations on the Reactions of a Rheumatic Group to an Epidemic Infection with Hemolytic Streptococcus of a Single Type, *J. Exper. Med.* 62: 159, 1935.)

†Note added at time of proof reading: Very recently these observers noted that patients having streptococcal infections followed by rheumatic recrudescences yielded strains of Group A hemolytic streptococci that were strong erythrogenic toxin and streptolysin producers while from another group of patients infected with streptococci but without rheumatic sequelae the strains of cocci isolated had neither the strong toxin nor hemolysin producing power. They feel, therefore, that the capacity of a given strain to produce certain poisons, together with the tendency of the patient to react in a peculiar manner to the infecting strain, are the requisite factors in the final rheumatic reaction. Their most recently expressed hypothesis appears to border closely on the allergic viewpoint discussed below.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. IV. Characteristics of Strains of Hemolytic Streptococcus, Effective and Non-Effective in Initiating Rheumatic Activity, *J. Clin. Investigation* 14: 755, 1935. Coburn, A. F., and Pauli, R. H.: Same series, VI. The Significance of the Rise of Antistreptolysin Level in the Development of Rheumatic Activity, *J. Clin. Investigation* 14: 769. Coburn, A. F., and Pauli, R. H.: Same series, VII. Splenectomy in Relation to the Development of Rheumatic Activity, *J. Clin. Investigation* 14: 783, 1935.

or intravenously.^{22, 23, 24, 25, 26} Several sets of statistics indicate that this is higher than in any other group of diseases. With one notable exception, patients with recent streptococcal infections show a similar heightened sensitivity; this exception is subacute streptococcal endocarditis,²⁶ where the reactivity might be designated as immune hypoergic, for indeed these patients show a high degree of resistance to introduction of living streptococci into their tissues. Rabbits subjected to repeated focal infections with streptococci of low virulence develop a state of hyperergy somewhat comparable to that seen in many rheumatic patients.^{27, 28} Animals immunized intravenously, on the other hand, show a state of hypoergy, also called immune allergy, similar to that of patients with subacute bacterial endocarditis.²⁹ On the basis of these observations we postulated³⁰ that the differences in the tissue reactivity of patients with rheumatic fever and of those with subacute bacterial endocarditis could be explained by differences in their "ergic" states. Subsequent work has shown that while the immune state in rabbits is rather closely related to the microorganisms with which the animal has been treated, the induced hyperergic state is very broad, both in respect of the manner in which it can be induced, and in the substances with which it may be detected; in other words, an animal made hypersensitive to a given strain of streptococci is also hypersensitive to distantly related strains, and even to irritating substances nonprotein in nature, and to physical traumatic insults. Of even greater interest is the observation that an animal may be immune to one type of streptococci and still show hyperergic manifestations when tested with some distantly related types.³¹ Numerous examples of this so-called allergic irritability³² might be cited, for we are learning that some allergic states are not necessarily so specific in all of their manifestations as once was thought to be the case.³³

These observations may have a direct bearing in rheumatic fever, for they may explain why such a high proportion of rheumatic patients have marked sensitivity to streptococcal products even though other signs of streptococcal infection are absent. Part of this increased sensitivity may be a manifestation of allergic irritability. This is suggested by the findings of Duckett Jones and Mote³⁴ that rheumatic patients show a high degree of sensitivity to intracutaneous injections of rabbit serum. Our³⁵ experience in confirming those observations has led us to the conception that rheumatic patients are unusually sensitive to many different injurious agents. Wilson's observation¹⁵ that her rheumatic patients were more subject to colds than a control group of a similar social status, might be interpreted in a similar manner: an altered state of reactivity of the tissues of these patients possibly rendered them more easily vulnerable to slight infections. If this conception is eventually confirmed, it gives a point of attack in trying to learn how the hypersensitive condition may be successfully removed. We still feel that all of the possible relationships between hyperergy and rheumatism have not been fully explored.

POSSIBLE FILTRABLE VIRUS ETIOLOGY

The failure of the previously discussed factors to explain completely and satisfactorily the pathogenesis of rheumatic fever has led many observers to the

opinion that the disease is due to an undiscovered filtrable virus. Gräff,³⁶ in Germany, has actively advanced this point of view for years, and Aschoff and Fahr and their followers have shown a tendency to agree with him, in opposition to Klinge's allergic theory.

We have not been unmindful of the validity of this hypothesis, and during the past fifteen years have tested it in numerous ways. Large numbers of the various species of laboratory animals have been injected with the following materials derived from patients with active rheumatic fever: blood, plasma, arthritic, pleural and pericardial exudates, cerebrospinal fluid, emulsions of subcutaneous nodules obtained at biopsy and of rheumatic tissues obtained post-mortem; nasopharyngeal exudates that had been obtained by washing the areas with Ringer's solution and also absorbed on cotton plugs that had been introduced into the nares of the patient and then transferred directly to the noses of monkeys. We have, in addition, employed culture media set up in different ways that have proved useful in growing known filtrable viruses. These materials have been injected intravenously, intraperitoneally, intracerebrally, intra-articularly, and subcutaneously; and in some instances we have used animals previously or concomitantly conditioned with streptococcal infections or immunizations. Detailed recital of these experiments would be superfluous in this place. Suffice it to say that aside from discovering, or helping to discover, some new diseases of laboratory animals, the results of these tests have been largely negative. Other workers have been equally unsuccessful in transmitting typical rheumatic fever to animals. The most obvious explanations of these failures are either that a virus was not present in the material used for attempted inoculation, or that the animals employed were not susceptible.

Very recently Schlesinger, Signy and Amies³⁷ have reported the obtaining from pericardial and pleural fluid of small particles that resemble the elementary bodies found in vaccinia, varicella, psittacosis, and some other virus-induced diseases. These elementary-like bodies were obtained by high-speed centrifugalization of exudates obtained from rheumatic subjects postmortem. When resuspended in formalised saline they were specifically agglutinated in the serum of ten rheumatic patients out of thirty-six tested. Patients yielding these agglutinating serums were in the active subacute or chronic stage of the disease; but the serums of patients with quiescent rheumatism were nonagglutinating; neither were those of patients with a number of other diseases.*

This interesting report contains the first positive evidence suggesting that a virus may have an etiologic relationship to rheumatic fever. It is noteworthy that antibodies were demonstrated *only* in serum from patients with *active disease*.

In this connection attention may be directed to the fact that the demonstration of antibodies, or rather the occurrence of what appears to be an antigen-antibody reaction, does not necessarily prove that either the antibody or the

*Very recently Coles has reported the observation of "virus bodies" in Giemsa stained films of pericardial and arthritic exudates from patients with rheumatic fever, and also in 25 out of 50 control pericardial fluids. No immunologic studies are recorded. *Lancet* 2: 125, 1935.

substance with which it reacts has an etiologic relationship with the diseased conditions under which they occur. For example: Tillett and Francis³⁸ demonstrated precipitins against the "C" substance of pneumococci in the serums of our patients during the acute febrile phases of rheumatic fever as well as in that of patients with lobar pneumonia, and with generalized staphylococcal infections. The high agglutinating capacity of the serums from patients with typhus fever for *Bacillus proteus* X-19 might also be recalled; but typhus is due to a member of the Rickettsia group of microorganisms.* Hughes³⁹ has shown that serums taken from monkeys recently recovered from severe yellow fever contain a precipitin capable of reacting with a precipitinogen which occurs in the blood of monkeys acutely ill with yellow fever. He definitely proved that this precipitinogen is not the virus of yellow fever, but that it appears to be associated with a protein of the albumin fraction, and is entirely independent of the protective antibody resulting from the infection. A similar precipitin, reacting with the precipitinogen in the blood of monkeys, was found in the serum of human beings recently recovered from severe yellow fever infection. In patients with infectious mononucleosis Paul and Bunnell⁴⁰ detected antibodies resembling what they described as heterophile antibodies. Recently Bailey and Raffel⁴¹ have shown that these hemolysins and agglutinins for sheep and ox red blood cells are not true heterophile or Forssman antibodies, but are probably the specific response to an antigen having a factor in common with a thermostable component of these erythrocytes, a certain strain of *B. Welchii* and possibly horse kidney.

In only one of these instances, involving bacteria, Rickettsia, filtrable virus, and unknown infectious agent, respectively, has it been shown that the antigen-antibody reaction involves part of a specific etiologic agent. Of extreme interest is the demonstration³⁹ that the tissues of an animal with yellow fever may become so altered that they act as true antigens and stimulate in that same animal the production of antibodies which have specific diagnostic significance, but no direct etiologic bearing. These examples are cited not in an effort to detract from the importance of the observations of Schlesinger and his co-workers, but to indicate the necessity for caution in accepting the evidence presented. These authors, moreover, state that their results simply tend to confirm the hypothesis that a virus may play an etiologic rôle, and suggest that if it does have this function it is only partly responsible for the disease manifestations, in which streptococci may act as the activating agents.

The synergic rôle of infectious agents in inducing diseases should, indeed, be kept in mind. The best established example of such a phenomenon is the combined action of a virus and a bacillus in bringing out the active symptoms of swine influenza.⁴² The virus of herpes labialis is carried by many a person for years with comparative impunity; but let him contract some other infection,

*Castaneda definitely established that there is an antigenic fraction of carbohydrate nature common to both the *Bacillus proteus* X-19 and the Rickettsia causing typhus fever. This is extractable from cultures of *Bacillus proteus* X-19 in the so-called X form, which gives precipitin reactions with both anti-Proteus X-19 serum and with the serum of patients who have had typhus fever as well as with that of horses hyper-immunized with Rickettsia.

The antigenic relationship between Proteus X-19 and *Typhus rickettsia*: 1. A Study of the Weil-Felix Reaction, *J. Exper. Med.* 58: 55, 1933. 2. A Study of the Common Antigenic Factor, *Ibid* 60: 119, 1934. 3. A Study of the Antigenic Composition of Extracts of *Bacillus Proteus* X-19, *Ibid*. 62: 289, 1935.

the blisters promptly appear; sunburn or hyperthermic therapy have similar activating effects on this virus; and certain phases of the menstrual cycle are regularly accompanied by the appearance of labial vesicles in some women. Herpes labialis is the best example of a virus-induced disease in which the infectious agent remains in the subject's body for long periods; although many students of this general class of diseases claim that persistence of viruses in the body is a characteristic phenomenon.

The assumption that a virus is etiologically significant in rheumatic fever, but requires some synergic influence for its activation would explain a number of previously observed features of the disease. While streptococcal infections apparently remain the most frequent precursors of an attack, infections such as measles or other exanthemas have been noted to play a similar rôle. We have seen an attack ushered in by antismallpox vaccination, and also other attacks apparently induced by such injuries as a sprained ankle or a bruised wrist. Bland and Duckett Jones⁴³ have reported that a febrile reaction following the intravenous injection of typhoid vaccine may have an effect similar to that of tonsillitis in setting off a rheumatic relapse, and have observed similar relapses following accidents and operations. The activating relationship of the menstrual cycle has already been mentioned; the parallism with herpes is obvious. Whether allergic irritability may result from virus infection is, as yet, unknown; and whether allergic states, induced by bacterial infections, are specially suitable for the development of some virus diseases must also be decided by future investigations.

In any event there is much evidence indicating that streptococcal infections must be seriously considered both in investigating the nature of rheumatic fever, and in its prevention and treatment. The devastating effect of some streptococcal epidemics in groups of rheumatic patients has been convincingly demonstrated.^{44, 45, 46} So far as we have been able to learn from carefully compiled statistics, severe pharyngitis or tonsillitis of apparent hemolytic streptococcal origin is liable to be followed by rheumatic relapses in 50 to 60 per cent of previously rheumatic subjects, while similar upper respiratory infections in nonrheumatic subjects are followed by rheumatic symptoms in less than 10 per cent of instances. These data indicate the importance of protecting the rheumatic subject from these infections; and doubtless the great difficulty in affording this type of protection to the dispensary and ward class of our population, when compared with persons in better economic circumstances, explains, in part, the relatively greater frequency of rheumatic fever among the former group. That good hygienic environments alone do not insure protection from this disease is illustrated by recent investigations in England, where hemolytic streptococcal epidemics among boys in boarding schools were followed by numerous cases of rheumatic fever, just as they are observed among children of the working classes.⁴⁷ While upon first glance the placing of rheumatic children in a tropical environment, where they do not suffer from severe streptococcal infection, would appear to offer useful prophylactic conditions, it is obvious that such extensive traveling and dislocation of family life that this would entail is out of the question for most persons suffering from this disease. It

appears, therefore, most important to devise and investigate other means whereby streptococcal infections may be rendered less devastating in rheumatic subjects.

SUMMARY

Rheumatic fever presents protean manifestations, which, when few in number, often make it difficult to distinguish the disease from closely related conditions; hence it is impossible to characterize the malady too accurately. The histopathologic picture, while presenting the well-recognized manifestations of inflammation, has certain peculiar features, chief of which are damage to the mesenchymal ground substance by some noxious agent the nature of which has not been definitely established; this damage is followed by hyperplasia and multiplication of primitive cells that often assume a definite architectural form. Inflammatory features are seen early in the rheumatic lesion in contrast to the initial cellular injury followed by the signs of inflammation usually seen in virus-induced diseases. The tissue of rheumatic patients appears to be unusually vulnerable to several injurious agents, and especially to substances contained in or derived from streptococci. Possibly this state of hypervulnerability, or allergic irritability, makes the tissues susceptible to the action of a hypothetical specific virus; on the other hand, the state of allergic irritability may be the result of prolonged action of such a virus, and the immediate attack may be merely set off by a bacterial infection or other traumatic insult. While much investigation remains to establish firmly and to correlate many of the phenomena discussed, the following working hypothesis remains to guide prophylaxis: It appears advisable to protect the rheumatic subject from certain bacterial infections as well as from other injurious and depressing influences if he is to be spared the repeated attacks of a disease that eventually lead to permanent cardiac disability, for repeated or recurring infections usually exert a more deleterious influence than does the initial attack.

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(For discussion see page 130.)

THE NATURAL HISTORY OF CHILDHOOD RHEUMATISM IN MINNESOTA*

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SINCE 1922 I have been in constant attendance at the Lymanhurst Heart Clinic to which the Minneapolis school physicians refer all children who present signs of cardiac disease. To this clinic, too, the school nurses have been instructed to send immediately on their return to school, all pupils who report their absence as having been due to an attack of rheumatism or chorea as well as all children who come to them complaining of leg pains. In 1926 Dowling School, a special school for orthopedic cripples, was opened to cardiac cripples and during the past nine years I have referred to this school 250 children suffering from heart disease. This group has been examined each week during the school year. Because this work has been carried on with the cooperation of the well-organized medical department of the school system, it has been possible to observe these rheumatic patients at the earliest opportunity and excellent follow-up work has also been possible. This study was undertaken to present the natural history of childhood rheumatism in this locality and to estimate the expected number of recurrences in a group of rheumatic children followed over a sufficient number of years. These control data are necessary in order to determine the efficacy of any type of specific therapy which might be tried in the future.

SUMMARY OF CASES STUDIED

Between 1922 and 1935, 1,868 patients have been examined at Lymanhurst (Table I). Of this number 160 had congenital heart disease, 27 extrasystolic arrhythmia, 23 neurocirculatory asthenia, 677 were found to have no heart

TABLE I
SUMMARY OF CASES EXAMINED AT LYMANHURST HEART CLINIC
1922-1935

Congenital heart disease	160
Extrasystolic arrhythmia	27
Neurocirculatory asthenia	23
No heart disease	677
Nonpathologic murmur	241
Rheumatics	713
1. Potential	405
2. Rheumatic heart disease	308
No diagnosis	27
Total	1,868

*From the Lymanhurst School Heart Clinic and Convalescent Cardiac Home.

disease, 241 presented murmurs which were considered nonpathologic in nature. There were 713 patients who gave a history of rheumatism and of this number 308 had valvular heart disease while 405 were considered as cases of potential cardiac disease. In 27 cases no diagnosis was made.

SEASONAL INCIDENCE

As has been pointed out by a number of investigators there is a distinct seasonal variation in childhood rheumatism. In Minneapolis, as shown by

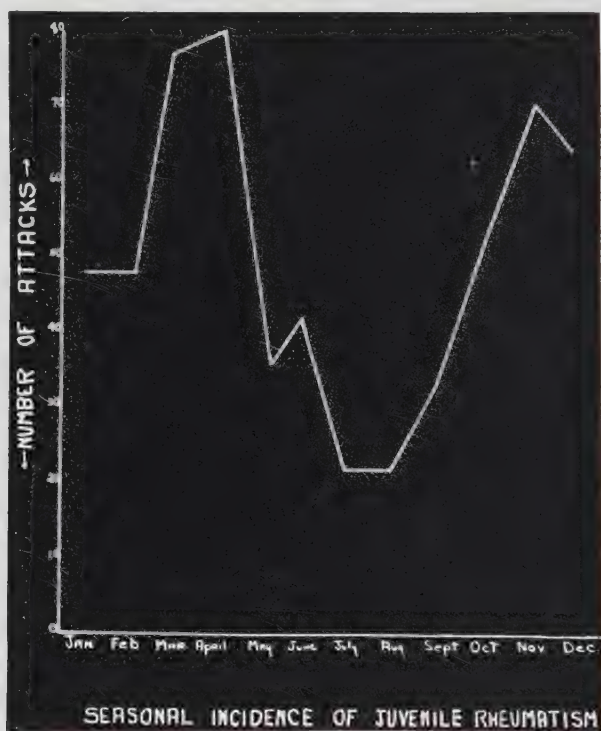


Chart 1.

Chart 1, there is a marked increase in the number of cases in the early spring and late fall. During the summer months rheumatic fever is at its lowest ebb. Other cities in the same geographic location have similar but not exactly the same seasonal variations in rheumatic incidence (Chart 2). It will be noted that the seasonal incidence in London, Philadelphia, and New York is practically the same as that in Minneapolis. In Scotland, however, the peak of incidence is in the fall months of October and November with no spring rise. The cause of this seasonal variation is not altogether clear. The seasonal increase in upper respiratory infections, and dietary deficiencies which are more prone to occur at the end of a long winter, have most often been suggested as possible reasons.

AGE INCIDENCE

Examination of our material indicates as shown by Chart 3 that the onset of childhood rheumatism most commonly occurs between the ages of five and six. This is a somewhat earlier peak of age incidence than is given by most other clinics and is explained by the fact that we have the opportunity of

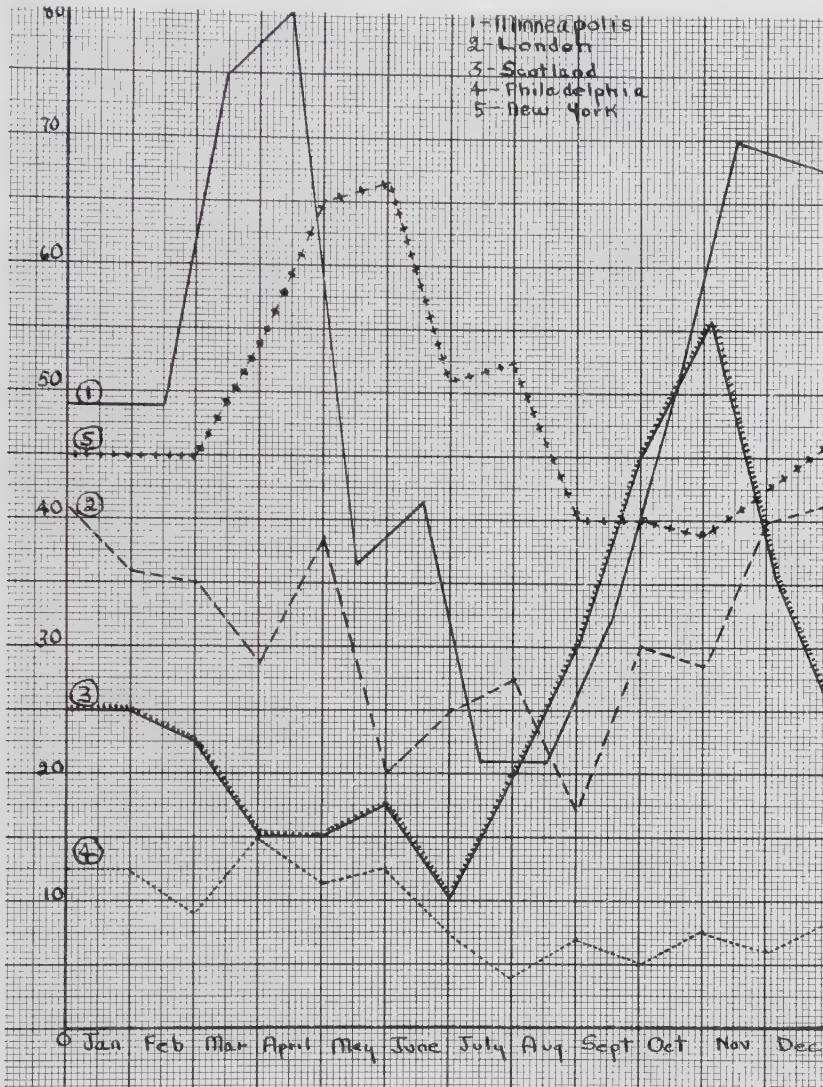


Chart 2.

examining most of our patients at the very onset of the disease. A number of patients have been observed who developed rheumatism during the first few years of life.

FAMILIAL TENDENCY

It has long been known that rheumatic fever is a markedly familial disease. Because of the importance of this phase of the problem our cases were studied

in this regard. During the year 1933 and 1934 all patients who reported to the clinic were questioned carefully concerning family history. Only the parents and siblings were included and care was taken to include in our data only cases which could be considered as childhood rheumatism. During this period 370 children were examined. Of this number, as shown in Table II, 201 gave a history of rheumatic disease, 120 of these patients already had rheumatic heart disease while 81 were potential cases, 67 had congenital heart disease, 44 nonpathologic murmur, 5 neurocirculatory asthenia, 6 extrasystolic arrhythmia, and 47 were found to have no heart disease. Of the 201 children who gave a history of rheumatism, 94 other members of their families gave

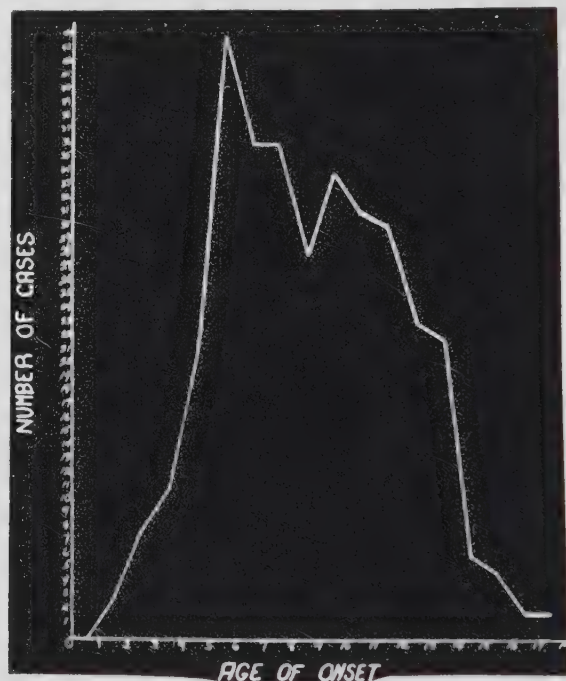


Chart 3.

a positive rheumatic history an incidence of 46.7 per cent, while among the 169 patients who gave a negative rheumatic history, 25 or 14.7 per cent of the other members of their families gave a positive history, indicating that the family tendency among the rheumatic children was three times as great as among the nonrheumatic control group. These figures do not give the complete picture of familial tendency in childhood rheumatism. It is not uncommon to find two or more members of the same family suffering from rheumatic fever at the same time. It has been suggested that rheumatic fever is a mildly contagious disease and a number of so-called epidemics have been described. Discovery of the etiology of this disease will eventually explain the marked familial tendency.

TYPES OF ONSET

In recent years a good deal has been written concerning the importance of allergy in rheumatism. It has been pointed out by a number of investigators that the great majority of children who develop rheumatic fever have a sore throat or upper respiratory infection a week or two before the rheumatism begins. The usual history, according to these investigators, is that the child develops the upper respiratory infection, apparently recovers, and then a week or two later suddenly develops rheumatism. The quiescent phase is explained as the period of developing sensitivity to the upper respiratory infection. During this past year all our patients have been studied in regard

TABLE II

FAMILY TENDENCY IN JUVENILE RHEUMATISM COMPARED WITH FAMILY TENDENCY IN NON-RHEUMATIC CHILDREN

DIAGNOSIS	CASES	TOTAL NUMBER OF CASES	FAMILY IN- CIDENCE	PER- CENTAGE
Rheumatic heart disease	120	201	94	46.7
Potential heart disease	81			
Congenital heart disease	67	169	25	14.7
Nonpathologic murmur	44			
Neurocirculatory asthenia	5			
Extrasystolic arrhythmia	6			
No heart disease	47			
Total number of cases ex- amined 1933-1934	370			

to the type of onset. Time-consuming careful histories were obtained from the patients and their parents. These children for the most part had recently recovered from an attack of rheumatism so the facts regarding onset were still clear in their minds. It was found (Table III) that of 201 children studied 27 or 13.5 per cent had a cold preceding the onset of rheumatism, 9 or 4.5 per cent had a sore throat, 4 or 2 per cent had pneumonia, 2 or 1 per cent had measles, 12 or 5.9 per cent developed rheumatism while convalescing from scarlet fever, 20 or 9.9 per cent had chorea before the rheumatism began, 9 or 4.5 per cent of the patients had various types of onset, 2 of these had infected fingers, 2 had abscessed ears, while 1 child injured himself on falling off a porch about ten days before the onset of an attack of rheumatic

TABLE III

TYPES OF ONSET OF JUVENILE RHEUMATISM

ONSET PRECEDED BY:	NUMBER	PERCENTAGE
Cold	27	13.5
Sore throat	9	4.5
Pneumonia	4	2.0
Measles	2	1.0
Scarlet fever	12	5.9
Chorea	20	9.9
Other	9	4.5
Gradual onset	90	44.8
Not obtained	28	13.9
Total	201	100.0

fever. However, 90 or 44.8 per cent of this group developed rheumatic fever gradually, with no preceding respiratory or throat infection. In many instances the patients and their parents were under the impression that the first involved joint was due to an injury while playing. A knee or ankle became swollen, this condition remained unchanged for a number of days while the child continued in school until gradually other joints became involved and the patient was forced to bed with a well-developed attack of rheumatic fever. As a result of this study one concludes that rheumatic fever may be preceded by an upper respiratory infection, but the most common type of onset is a gradual one not preceded by any infectious process.

RHEUMATIC AND NONRHEUMATIC LEG PAINS

All investigators concerned with the problem of rheumatic infection in children are troubled considerably by the history of leg pains. It is difficult to determine which of these children complaining of leg pains are suffering from rheumatic infection and are in danger of developing rheumatic heart disease, and which have no rheumatic infection. It has long been taught that all children who complain of leg pains are rheumatic and potential cardiaes. The public especially has been led to believe that such leg pains are of serious moment, they have been informed that there is no such thing as "growing pains" but that these pains are rheumatic in nature. As a result, numerous such children have had their tonsils removed, some have been confined to bed for long periods of time because of "beginning heart disease" and no doubt a good number of them have had convalescent home care. As a result of our experience over the past twelve years, it is our impression that the great majority of children who complain of leg pains are not suffering from rheumatism and are in no danger of developing heart disease. In an attempt to classify children who complain of pains in the extremities, a differential diagnostic table has been worked out (Table IV) based on clinical observation. A group of known rheumatic children attending Dowling School have been studied in regard to the type of leg pains from which they complained, and these findings have been compared with the symptoms presented by children complaining of leg pains only and who have never had rheumatic fever. Known rheumatic children have more or less constant pain in their joints even while they are up and about and are apparently well. They complain mostly during the day, the pain is intensified on motion, there is difficulty in walking and a limp is often noted. These symptoms ordinarily disappear when the patient goes to bed and rarely do these rheumatic children complain during the night. On the other hand, nonrheumatic children complaining of leg pains have most of their difficulty after going to bed; they commonly awake two or three hours after retiring, and the pain is intense enough to cause them to cry. Heat or massage of the muscles usually causes the pain to disappear, and the child is again able to fall asleep. On arising in the morning the nonrheumatic children are free from pain and complain of no stiffness on walking. The rheumatic children, on the other hand, while they do not complain of leg pains during the night have difficulty in walking when first arising and complain of stiffness for an hour or two in the morning. The

rheumatic children while they may also have muscle pain usually point out the maximum point of pain in the joints themselves, while the nonrheumatic group complain mostly of pain in the muscles of the lower extremities and are unable to locate any point of maximum pain. On being asked to locate his pain the nonrheumatic child will run his hand over the entire lower extremity while the rheumatic patient points directly to his knee, ankle, or elbow joint. The nonrheumatic patient rarely has pain in the upper extremities, the rheumatic child almost always complains of difficulty in all four extremities at one time or another. The nonrheumatic child complaining of leg pains is usually in good health and commonly comes from families in better economic circumstances while the known rheumatic child is usually in poor health and comes from poorer families. The rheumatic child presents other signs of rheumatic activity such as low-grade fever, frequent nosebleeds, pallor, unexplained abdominal cramps, and undernourishment. Frequently, examination of the involved joints in the rheumatic children will reveal local increased temperature, no such findings are present in the nonrheumatic group. A large group of patients complaining of leg pains have been observed for a number of years and will be reported at a later date. It can be noted here, however, that this clinical differentiation has worked well in our experience as almost without exception the children considered as nonrheumatic have not developed signs of cardiac disease. The necessity for differentiating the rheumatic from the nonrheumatic child becomes more and more important as our facilities for treating early cases improves. In a short experience in our Convalescent Home at Lymanhurst we have had to face this problem practically. If care is not taken in selection of patients, a good number of

TABLE IV

DIFFERENCES BETWEEN NONRHEUMATIC "GROWING PAINS" AND JOINT PAINS OF SUBACUTE RHEUMATIC FEVER

	NONRHEUMATIC "GROWING PAINS"	JOINT PAINS OF SUBACUTE RHEUMATIC FEVER
Time of pain	Soon after going to bed. Pain gone in morning. No pain on motion.	Worse on arising. Exaggerated on motion. Difficulty in walking, may cause limp. Pain present during most of day, disappears on getting warm in bed.
Location of pain	In muscles of thighs and legs. Child vague in pointing out site of pain.	In joints themselves. Child points directly to knees or ankles. Often complains of pain in joints of upper extremities also.
General health	Usually good	Usually poor
Other signs of rheumatic activity	Usually none	Common, may have frequent nosebleeds, unexplained fever, pallor, abdominal cramps, undernourishment. Evidence of carditis.
Objective findings in joints	None	Often joints are slightly swollen and hot
Family history of juvenile rheumatism	Uncommon	Very common

nonrheumatic children will be admitted to convalescent homes where they do not belong. The differential diagnosis between the rheumatic and non-rheumatic child is not always easy, and it is our impression that this chart based on clinical observations will tend to assist in making this differentiation.

EXPECTANCY OF RECURRENCES

In order to determine whether or not any specific type of treatment is effective in such a chronic infectious process as juvenile rheumatism, it is necessary first to know what may be expected in a group of untreated patients followed over a number of years. The normal expectancy of recurrences in a group of children with rheumatism has therefore been studied. As indicated in Table V of a total number of 342 rheumatic children, 178 or 52.1 per cent were found to have had one attack only, while 164 or 47.9 per cent of these children had recurrent attacks. Of the 164 patients with recurrences it was found that 44 or 26.8 per cent recurred at the end of the first year while a similar number had recurrences after two years, making a total of 88 patients or 53.6 per cent who had recurrences after two years. Twenty-eight or 17.1 per cent of these children recurred at the end of three years, 20 or 12.2 per cent after four years, and 5 or 3.1 per cent after five years, making a total of 141 children or 86 per cent who had recurred at the end of five years. As the result of this study, it is fair to conclude that it will be necessary to

TABLE V
INCIDENCE OF RECURRENCES IN JUVENILE RHEUMATISM

Total number of rheumatic children examined		342		
Children with one attack only		178 or 52.1%		
Children with recurrent attacks		164 or 47.9%		
RECURRENCES WITHIN	NUMBER	PER CENT	TOTAL	PER CENT
1 year	44	26.8	44	26.8
2 years	44	26.8	88	53.6
3 years	28	17.1	116	70.7
4 years	20	12.2	136	82.9
5 years	5	3.1	141	86.0
6 years	8	4.9	149	90.9
7 years	4	2.4	153	93.3
8 years	5	3.1	158	96.4
9 years or more	6	3.6	164	100.0

follow a group of treated rheumatic children a minimum of five years before any definite conclusions can be drawn. In a number of instances reports have occurred in the literature, giving results of treatment with vaccine for two or three years. As indicated by these figures such reports cannot be altogether conclusive until these patients have been followed a minimum of five years. A detailed study has been made of recurrences in our rheumatic children so that we have excellent control material to use for comparison in any group of children treated in the future.

ANALYSIS OF PATIENTS DEAD OF RHEUMATIC DISEASE

Table VI gives a résumé of the findings in the 34 children of our group that are known to be dead. Undoubtedly the follow-up study which we are

now carrying on will discover many more deaths. It will be noted that in nine instances while these patients were known to have died of rheumatic heart disease, no history of rheumatism was obtained, so that the length of illness from the beginning of the rheumatic process to death could not be

TABLE VI

NO.	SEX	AGE AT DEATH	CAUSE	AGE AT FIRST ATTACK	RECUR- RENCES	TON- SILS	X-RAY	DIAG- NOSES	FAM- ILY	TIME ILL	YEAR DIED
1	M	7- 6	R.H.D.			In	+	M.R. + M.S.	-	None	25
2	F	11- 6	R.H.D.			In	++	M.R. - M.S. - A.R.	+	None	27
3	M	17-10	R.H.D.	2-1 (Rh)	1. 6-11 (Ch)	6-7	+++	M.R. + M.S.	+	15-9	29
4	M	15- 1	R.H.D.	9-2 (Ch)		In	++	M.R. + M.S.	+	5-11	25
5	M	12-10	R.H.D.	4-9	1. 5- 7 2. 11- 4	In	None	M.R. + M.S.	-	8-1	25
6	F	17- 5	R.H.D.	9-5	1. 12- 7	9-6	++	M.R. + M.S.	-	8-0	32
7	F	13- 2	S.A.B.E.	9-0	1. 13- 0	5-3	++	M.R. + M.S.	+	4-2	28
8	M	13-11	R.H.D.	10-0	2. 10-11	2-5	+++	A.R. + A.S. + M.R. + M.S.	-	3-11	29
9	F	14- 9	R.H.D.	9-8		3-1	+++	M.R. + M.S.	-	5-1	34
10	M	16-10	R.H.D.	9-6	1. 11- 2	6-3	+++	M.R. + M.S.	-	7-4	34
11	F	9- 7	R.H.D.	4-9 (Ch)	1. 8- 7 (Rh & Ch)	In	+++	M.R. + M.S.	+	4-10	30
12	F	18- 0	R.H.D.			8-6	++	M.R. + M.S.	-	None	34
13	M	12- 1	R.H.D.	7-10 (Rh & Ch)	1. 11-10 (Rh)	In	-	M.R. + M.S.	-	4-3	27
14	F	15-10	R.H.D.			In	+++	M.R. + M.S.	+	None	26
15	F	13- 4	S.A.B.E.	7-0		9-11	-	Potential	-	6-4	32
16	M	15- 2	R.H.D.			7-11	++	M.R. + M.S.	+	None	32
17	F	12- 9	R.H.D.	6-10	1. 7- 7 2. 9- 0 3. 11- 1	9-5	++	M.R. + M.S. + A.R.	+	5-11	32
18	F	20- 1	R.H.D.			Out	+++	M.R. + A.R.	-	None	32
19	M	16- 8	R.H.D.	7-7	1. 9-10 2. 10- 9	11-2	+++	M.R. + A.R. + A.S.	-	9-1	30
20	M	8- 9	S.A.B.E.	4-7	1. 8- 7	8-7	-	M.R. + M.S.	-	4-2	34
21	F	17- 7	R.H.D.	12-9		15-7	+++	M.R. + M.S.	-	4-10	29
22	M	16- 7	S.A.B.E.	13-9		14-0	+++	M.R. + M.S.	-	2-10	29
23	M	15-11	R.H.D.	12-11		10-9	+++	M.R. + M.S.	-	3-0	27
24	M	15- 5	R.H.D.	8-5 (Ch)	1. 10- 6 (Ch)	8-6	+++	M.R. + M.S.	-	7-0	29
25	M	14- 6	R.H.D.	9-6		In	None	M.R. + M.S. + A.R.	-	5-0	27
26	F	14-10	R.H.D.			In	+++	M.R. + M.S.	+	None	30
27	M	11- 1	R.H.D.			8-9	-	M.R. + M.S.	+	None	23
28	F	5- 4	R.H.D.			In	+	M.R.	-	None	27
29	F	13- 8	R.H.D.	10-5	1. 10- 9 2. 13- 7 3. 10- 9	In	+	M.R.	-	3-3	33
30	F	12- 6	S.A.B.E.	5-11 (Ch)	1. 7-10 2. 8-11 3. 10- 9	6-8	++	M.R. + M.S. + A.R.	-	6-7	30
31	M	11- 4	R.H.D.	10-5		8-4	None	M.R. + M.S.	-	0-11	31
32	M	14- 2	R.H.D.	10-10	1. 11- 4 (Ch) 2. 12- 3 3. 14- 1	11-2	++	M.R. + M.S.	-	3-4	29
33	F	16- 2	R.H.D.	9-0		9-4	++	M.R. + M.S.	+	7-2	33
34	F	13- 5	R.H.D.	6-9	1. 12-7 (Rh & Ch)	8-8	+	M.R. + M.S.	+	6-8	33

determined. Five patients with rheumatic heart disease died of subacute bacterial endocarditis. Most of these children had repeated attacks of rheumatic fever and chorea, the great majority of them had greatly enlarged hearts as indicated by x-ray examination. The average number of years that these patients lived after the onset of rheumatism was about six years. Two-thirds of these children who died had had their tonsils removed.

CONCLUSIONS

1. Rheumatic disease in children in Minneapolis is essentially the same as in other centers throughout the world.

2. Rheumatic fever is more prevalent in Minneapolis in the early spring and late fall. During the summer the disease is at its lowest ebb. Similar curves from other large centers are presented.

3. Childhood rheumatism occurs most commonly between five and six years of age.

4. This disease is definitely familial. The familial tendency is three times as great in a rheumatic group as in a nonrheumatic group.

5. Rheumatism in children in a considerable number of instances follows an upper respiratory infection, but most commonly develops slowly with no preceding infectious process.

6. The great majority of children who complain of leg pains are not suffering from rheumatism. A differential diagnostic table based on clinical observations is presented.

7. The normal expectancy of recurrences of rheumatism has been determined. This material is to be used as a control in determining the efficacy of any type of specific treatment which might be tried in the future.

8. An analysis of the findings of 34 children who have died is presented.

DISCUSSION ON PAPER OF DR. H. F. SWIFT, "THE NATURE OF RHEUMATIC FEVER," AND PAPER OF M. J. SHAPIRO, "THE NATURAL HISTORY OF CHILDHOOD RHEUMATISM IN MINNESOTA"

DR. JOHN WYCKOFF, NEW YORK, N. Y.—The very careful study of Dr. Shapiro is one of the many which have built up the clinical picture that Dr. Swift has so ably reviewed. Each such study has added some new knowledge. Of special interest is Dr. Shapiro's study of the various types of pain, especially in the legs of growing children, some of which are probably rheumatic and some of which are not.

About every two or three years we have learned to expect a comprehensive survey of rheumatic fever by Dr. Swift, a master of the subject. He again brings to our attention certain things which we must hold in our minds; the fact that the disease is extremely complex, and that it is very difficult to say clinically what is rheumatic fever and what is not. He has reviewed the later studies on structural change and has discussed the etiology. I wonder how many times Dr. Swift has come to Atlantic City and has had to listen to a new idea on the etiology of rheumatic fever, has had to act in a receptive mood, and not appear bored.

DR. RALPH KINSELLA, ST. LOUIS, MO.—I feel personally much indebted to Dr. Shapiro for discussing the subject of growing pains. He has made a comprehensive contribution to it.

It is difficult to discuss the subject of Dr. Swift's paper, the etiology of rheumatic fever. My experience is limited to that which concerns the relationship of streptococcal infections with rheumatic fever.

Not every infectious disease has the pattern of a simple, unique reaction such as lobar pneumonia has. There are many infections which have more than one phase, and a capacity for two phases is easily seen in many coccal infections. The double pattern was forecast in miniature, so to speak, in the experiment of Dr. Swift in which he observed a primary exudative reaction to the intradermal injection of living streptococci and a secondary proliferative reaction in the same site without any further manipulation of the animal. The proliferative reaction may continue in the animal due to the continued presence of the exciting agent.

There is no experimental infection as similar to a rheumatic infection, as far as topographic arrangement is concerned, as one by *Streptococcus hemolyticus* or non-hemolyticus. It is possible to establish a chronic infection in animals, in the case of dogs, by infecting the heart valve and in the case of rabbits, by infecting the knee joint; one can keep a continued infection in the animal's body in this way. In the course of time there will be developed proliferative lesions throughout the body that assume a topographic and histologic arrangement like acute rheumatic fever. Some believe it to be identical with rheumatic fever. However, I think the two conditions remain sharply separated as yet.

The proliferative stage of rheumatic fever or of any disease, is probably one that depends for its continuance on the continued presence in the body of the exciting agent; in this case not yet discovered. This mechanism of reacting in a proliferative way seems to be easily set off in some subjects and follows quickly upon the injury to cells produced by virus. The studies of Dr. Shapiro invite the thought that probably children have some change in their internal environment, as far as bacterial agents are concerned, which may depend on hereditary factors.

THE RELATIONSHIP BETWEEN RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS*

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DURING the past century there existed considerable controversy over the relationship between rheumatic fever and rheumatoid arthritis. Opinion was more or less equally divided into two schools, those who believed that the two were separate and distinct diseases and those who maintained that they were different expressions of the same fundamental process. At the present time the majority of clinicians both in this country and in Europe consider these two clinical entities as distinct diseases having little or no relation to one another. Occasionally, however, the opinion is still expressed that the two are intimately related and possibly different manifestations of the same process. This is particularly true in the German literature where the relation between the two conditions is constantly discussed.

Older Conceptions.—The evolution of opinion regarding the relationship of rheumatic fever and rheumatoid arthritis is of considerable interest. Bal-lonius,¹ in 1642, seems to have been the first to differentiate between rheumatism and arthritis but it was largely due to the teaching and writings of Haygarth² (1805) and Heberden³ (1810) that the two came to be regarded as separate diseases. Even at this early date, however, contrary opinions were held and, in his excellent description of rheumatoid arthritis, Scudamore⁴ (1827) stated that this disease was merely a variety of "chronic rheumatism." During the remainder of the nineteenth century opinion as to the relationship of the two seems to have been more or less evenly divided between the two schools. Among those who believed that they were distinct entities may be mentioned Fuller⁵ (1852), Adams⁶ (1857), A. B. Garrod⁷ (1859), Fagge⁸ and Bristowe.⁹ Contrary opinions were expressed by Watson¹⁰ (1836), Todd¹¹ (1843), Hutchinson¹² (1881), Charcot¹³ (1881), Sir Dyce Duckworth¹⁴ (1884), Mitchell Bruce¹⁵ (1894), and Hawthorne¹⁶ (1900). Todd, in 1843, stated: "Chronic rheumatism of the joints is clearly traceable to a rheumatic state of the constitution." Duckworth, in 1884, wrote: "The disease (rheumatoid arthritis) is a true form of rheumatism" and "one of the several manifestations of the rheumatic branch of the basic arthritic diathesis." According to Mitchell Bruce, "the two diseases are expressions of one morbid process which differ from each other partly in intensity and partly in the manner of their evolutions." Charcot stated: "There are not two fundamentally distinct diseases to be dealt with as certain authors fancy,

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The Arthritis Clinic of the Presbyterian Hospital is supported by the Faulkner Memorial Fund.

but only two manifestations of one and the same diathetic state." In a monograph entitled "Rheumatism, Rheumatoid Arthritis and Subcutaneous Nodules," Hawthorne (1900) discussed at length the relationship between the two diseases. He concluded that the presence of similar subcutaneous nodules in both rheumatic fever and rheumatoid arthritis indicated an intimate relationship between the two conditions.

Modern Conceptions.—In more recent times there has been a pronounced tendency on the part of American and English clinicians to regard the two as separate and distinct diseases although occasional contrary opinions are still expressed. Thus Clarke¹⁷ (1915) considers the similar geographic distribution of rheumatic fever and rheumatoid arthritis as being indicative of a relationship between the two. Hare¹⁸ (1928) refers to both rheumatic fever and rheumatoid arthritis under the term "rheumatic disease" and states: "I would advance a more catholic outlook upon rheumatic disease, which, in essentials, remains but one of various inflammations of vascular connective tissue." In a report on "The Relation of Orthodox Rheumatic Infection to Multiple Infectious Arthritis" Coates¹⁹ (1930) presents statistics on the incidence of frank rheumatic manifestations in patients with rheumatoid arthritis and in immediate members of their families. While not drawing any definite conclusions he considers that the figures are, to say the least, significant.

In the German and Scandinavian literature a somewhat different opinion prevails. Here the relation of the two diseases is widely discussed and clinicians have found it convenient to divide rheumatoid arthritis into two groups: (1) primary chronic polyarthritis and (2) secondary chronic polyarthritis. The second group comprises those cases which develop as a sequel to rheumatic fever. The recognition of a group of cases intermediate between rheumatic fever and rheumatoid arthritis is very general among German clinicians and a similar point of view is held by the Scandinavians. Freund²⁰ believes that, in spite of the similarities between the two, they should be separated for clinical purposes. Fischer²¹ is of the opinion that the two are intimately related and that such differences as do exist can be attributed to the varying degrees of immunity possessed by the host. He particularly stresses the fact that there are many transitional cases and that it is frequently impossible to separate the two. Kahlmeter²² states: "In my opinion, therefore, there is a great deal in favor of rheumatic fever and chronic rheumatoid arthritis being due to a pure infection of the same virus and that the different clinical pictures exhibited depend upon differences in the virulence of the infection and upon the different mode of reaction, temporary or constant, of this virus." Klinge and Grzimek,²³ after extensive investigations on the histopathologic changes in the two diseases, conclude that they are one disease process with different phases and with different clinical and anatomic manifestations in each individual phase.

It is apparent from the foregoing résumé that the current tendency in American and English clinical medicine to regard rheumatic fever and rheumatoid arthritis as separate and distinct diseases does not meet with universal favor. In the present communication evidence will be offered in support of the hypothesis that the two diseases are intimately related and possibly

different manifestations of the same fundamental pathologic process. The following phases of the problem will be considered: (1) Familial relationship; (2) geographic distribution; (3) initiating factors; (4) seasonal incidence; (5) age incidence and clinical manifestations in different age periods; (6) pathologic similarities; (7) immunologic findings.

1. *Familial Relationship*.—It is well known that orthodox rheumatic fever exhibits a marked familial tendency. The statistics of different authors vary somewhat but careful studies show that more than one member of the family is affected in between 37 and 50 per cent of cases (Draper and Seegal,²⁴ Faulkner and White,²⁵ St. Lawrence²⁶). It is somewhat less generally appreciated that rheumatoid arthritis also shows a definite familial incidence. In a recent study of 100 cases in our clinic, an immediate member of the family was similarly affected in 15 instances. Of more significance, however, is the fact that rheumatic fever and rheumatoid arthritis tend to occur in the same families. In a study of the family history of 50 cases of rheumatoid arthritis, Coates¹⁹ found that in 16 cases (32 per cent) an immediate member of the family suffered from rheumatic fever. In our own series of rheumatoid arthritis cases the incidence of proved, orthodox, rheumatic infection in the immediate family was 14 per cent. Although considerably less than Coates' figures this is at least fifteen times greater than normal expectancy. It must therefore be concluded that rheumatic fever and rheumatoid arthritis tend to occur in the same families. This observation may be interpreted in a variety of ways and assumes significance only in connection with the other evidence of a relationship between the two diseases.

2. *Geographic Distribution*.—Evidence is available to show that rheumatic fever is essentially a disease of the temperate zones. Its incidence diminishes the farther one goes south and it is a relatively rare event in the tropics. (Seegal and Seegal,²⁷ and Coburn.²⁸) Complete data on the geographic distribution of rheumatoid arthritis are not available but the reports of certain observers are significant. The statistics collected by Clarke¹⁷ from the British Army and the Colonial Medical Services show the same geographic distribution for rheumatoid arthritis as for rheumatic fever. For example, the records of the Federated Malay States show that of 71,208 patients treated in one year no case of rheumatoid arthritis appears. The Straits Settlement Medical Report for the same year presents an analysis of 113,509 patients treated in various tropical countries from Nyassaland to Singapore and in only one instance is the occurrence of rheumatoid arthritis recorded. Clarke analyzed the government returns for two years in thirteen tropical countries and found that out of 1,000,000 in-patients not one was diagnosed as rheumatoid arthritis. Examination of the medical reports of the United Fruit Company, whose estates are largely located in tropical countries, shows little evidence of the occurrence of rheumatoid arthritis. Finally, the reports of several observers in Porto Rico and Jamaica indicate that both rheumatic fever and rheumatoid arthritis are relatively rare events in those islands.

The similar geographic distribution of rheumatic fever and rheumatoid arthritis is a matter of considerable interest. So far as we are aware the only

other example of a specific disease which is equally rare in the tropics is that of scarlet fever. It is true that the incidence of both diphtheria and poliomyelitis diminishes in southern latitudes but both of these diseases have appeared in epidemic form in the tropics. In any case, as Clarke has stated, "the concurrent absence of both rheumatic fever and rheumatoid arthritis in the tropics contrasts so markedly with their concurrent presence in temperate climates that it has left the impression that there may be a causal connection between the two diseases."

3. *Initiating Factors.*—The relation between infection of the upper respiratory tract and the initiation of the rheumatic process is well established. There is general agreement that the relationship is too constant to be a mere chance occurrence. In rheumatoid arthritis the relation is less clear and there are many who will doubt its importance. Nevertheless, conspicuous examples are from time to time observed in which the disease appears to be undoubtedly ushered in by a preceding attack of tonsillitis or sore throat. In our experience

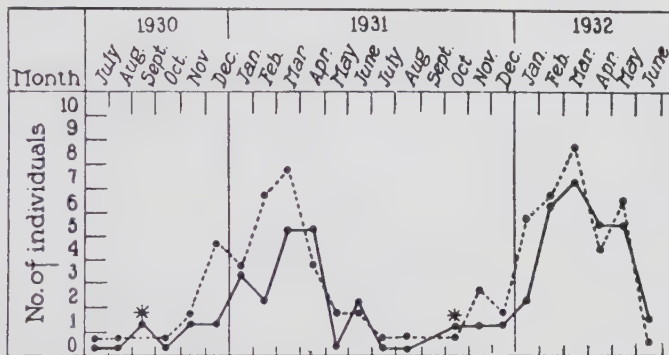


Fig. 1.—Seasonal incidence of hemolytic streptococcus pharyngitis and recrudescences of rheumatism among 165 ambulatory rheumatic subjects in New York City. The peaks occurred during the spring months, and were followed by a rapid rise in the incidence of recrudescences among ambulatory rheumatic subjects. (After Coburn.)

..... indicates hemolytic streptococcus pharyngitis.

— indicates acute rheumatic fever.

*Throat cultures not obtained during September, 1930 and 1931. Patients experienced preceding pharyngitis.

such examples are encountered more frequently than is generally supposed. Approximately 20 per cent of cases give a definite history of such infection and in a further 20 per cent a more equivocal history can be obtained. It is our belief that preceding infection of the upper respiratory tract constitutes one of the most important factors in the initiation of the disease rheumatoid arthritis.

4. *Seasonal Incidence.*—In the United States and Canada rheumatic fever exhibits a definite seasonal incidence, reaching a peak in the month of March. This is true not only for the initial attacks but also for subsequent exacerbations. The seasonal incidence of rheumatic recrudescences together with the seasonal incidence of hemolytic streptococcal pharyngitis is shown in Fig. 1. In such a chronic and insidious disease as rheumatoid arthritis, it is more difficult to speak of a seasonal incidence. However, a careful study of cases in New York City reveals a seasonal incidence which corresponds closely with that of rheumatic fever. The month of onset in a series of 68 cases in which the time of

onset could be accurately determined is shown in Fig. 2. This similarity in the seasonal incidence of the two diseases constitutes a further link in the chain binding the two conditions together.

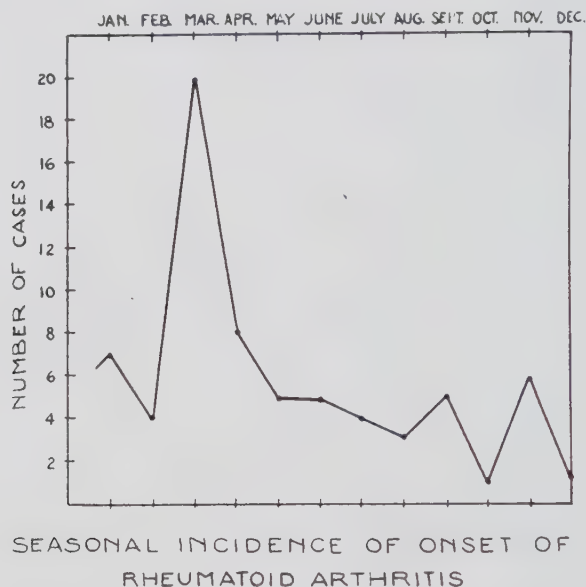


Fig. 2.

AGE AT ONSET

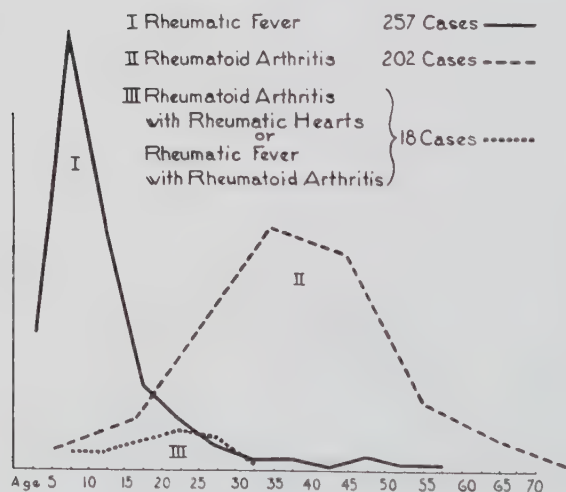


Fig. 3.

5. *Age Incidence and Clinical Manifestations of the Two Diseases in Different Age Periods.*—Rheumatic fever is essentially a disease of childhood while rheumatoid arthritis is predominantly a disease of adult life. The age of onset of 257 cases of rheumatic fever and 202 cases of rheumatoid arthritis is shown in Fig. 3. It will be observed that in nearly 90 per cent of the patients the onset of

rheumatic fever occurs before the age of fifteen while in over 90 per cent of the patients the onset of rheumatoid arthritis occurs after the age of fifteen. More significant, however, is the fact that the clinical manifestations of the two diseases differ widely in different age periods. It is well recognized that rheumatism in childhood presents a different picture from that seen in adult life. As long ago as 1889, Cheadle²⁹ wrote: "In the rheumatism of early life arthritis is at its minimum; endocarditis, pericarditis, chorea, and subcutaneous nodules at their maximum. As life advances this is gradually reversed; the joint affection becomes prominent, constant and typical of the disease and reaches its maximum; while the other phenomena decline and tend to die out." A summary of the clinical manifestations of rheumatic fever at various age periods is presented in Table I.

TABLE I

CLINICAL MANIFESTATIONS OF RHEUMATIC FEVER AT VARIOUS AGE PERIODS (AFTER COBURN)

INFANCY		CHILDHOOD	
<i>Pancarditis</i>	++++	<i>Pancarditis</i>	++++
Vague symptoms	++	Epistaxis	++++
Pallor	++	Vague symptoms	++++
Chorea	+	Erythemas	+++
etc.		Chorea	+++
		Subcut. nodules	++
		<i>Polyarthritis</i>	++
		etc.	
YOUNG ADULT		ADULT	
<i>Polyarthritis</i>	++++	<i>Chronic arthritis</i>	+++
Epistaxis	++	<i>Polyarthritis</i>	+++
Vague symptoms	++	Pancarditis	±
<i>Pancarditis</i>	++	etc.	
Erythemas	+		
Subcut. nodules	+		
<i>Chronic arthritis</i>	+		
etc.			

The clinical picture of rheumatoid arthritis is more constant in various age periods than that of rheumatic fever, but it also shows significant variations. Attention is called to the occurrence of carditis in classical cases of rheumatoid arthritis, a more frequent event than is generally recognized. In our clinic we have observed 22 examples of this condition and, in a series of 100 consecutive cases, 7 were found to have unequivocal signs of rheumatic heart involvement. It is of special significance that the onset of all these cases occurred in the earlier decades of life, in the majority of instances between the ages of fifteen and twenty-five. Reference to Fig. 3 will show that this is the age period intermediate between that of rheumatic fever and rheumatoid arthritis.

In the minds of many observers the occurrence of typical rheumatoid arthritis in children and the undoubted examples of the development of classical rheumatic fever in the later decades of life may constitute a formidable argument against the hypothesis which is here being presented. In this connection, however, attention should be called to certain facts. In the first place, rheumatoid arthritis in children, or Still's disease, is a relatively rare condition. In a six-year period, during which over 800 cases of rheumatoid arthritis have been observed in

our clinic, only 10 patients under twelve years of age have been seen. In the second place, rheumatoid arthritis in children may at times appear as a fulminating infection accompanied by acute joints, high fever, marked leucocytosis and occasionally pericardial involvement. McCrae³⁰ described two cases in which pericardial effusion was so marked that tapping was necessary. In three of the cases originally described by Still³¹ complete synechia of the pericardium was found at autopsy. It is difficult to offer any explanation for the infrequency of endocardial involvement in Still's disease but, by general consent, pericarditis is one of the most characteristic of all the manifestations of orthodox rheumatic infection. With regard to the development of orthodox rheumatic infection late in life attention is directed to two facts. In the first place, such cases are relatively rare. In the second place, it is exceedingly difficult, even impossible, to be certain that a prior infection has not occurred in the earlier decades of life.

Reference has already been made to the occurrence of rheumatic heart involvement in rheumatoid arthritis. Attention is also directed to the fact that chronic joint changes do develop fairly frequently as a sequel to rheumatic fever. In the German and Scandinavian literature it is customary to refer to these cases by the term "secondary chronic polyarthritis." Freund²⁰ refers to 110 cases in his own experience while Fischer²¹ describes 202 cases. While such an incidence suggests that the disease picture in Europe may be somewhat different from that with which we are familiar in this country, examples of this form of rheumatic disease are not infrequently encountered in a large outdoor clinic. The following statistics from Fischer's clinic on the differentiation of "primary chronic joint rheumatism" (rheumatoid arthritis) and "secondary chronic joint rheumatism" are also of interest. He states:

1. The "primary" form shows its maximum two decades later than the "secondary" form.
2. The "primary" form leads more frequently (52 per cent) to ankylosis and deformity than the secondary form (37 per cent).
3. Cardiac involvement occurs much more frequently (65 per cent) in the secondary form than in the primary form (4 per cent).

Finally, brief mention should be made of those cases in which a differential diagnosis of the two conditions cannot be readily made. It is commonly stated that the disease, rheumatic fever, responds to salicylates, is associated with carditis, and leaves no permanent disability of the joints. Rheumatoid arthritis, on the other hand, does not respond to salicylates, is not associated with carditis and almost invariably proceeds to a permanent disability of the joints. It has already been shown that two of these criteria possess only a relative value and reference will now be made to the third differential point, the different effect of salicylates.

In the minds of many the different effect of salicylates constitutes one of the most fundamental distinctions between rheumatic fever and rheumatoid arthritis. It must be pointed out, however, that salicylates have no effect on the course of events in rheumatic fever except on the exudative manifestations and

as antipyretics. They are quite without effect in the proliferative stage of the disease during which cardiac manifestations are so prone to occur. Furthermore, the effect of salicylates is less dramatic in adults than in children and is occasionally quite disappointing. Finally, salicylates are the most universally used of all drugs in the treatment of rheumatoid arthritis, as well as of rheumatic fever, and, while rarely so dramatic in the former condition, their administration is frequently attended by the greatest symptomatic relief.

It will be admitted by all that, among large groups of rheumatic fever and rheumatoid arthritis patients, many borderline cases occur. They are most commonly observed in the late adolescent and early adult years and are more frequently encountered among ambulatory out-patients than among hospital patients. In our own clinic this type of case is not infrequently seen and defies precise classification in spite of all clinical and laboratory examination.

6. *Pathologic Similarities.*—The most convincing evidence of a relationship between rheumatic fever and rheumatoid arthritis is to be found in the pathologic changes. In the present paper reference will be made only to the similarity of the subcutaneous nodules and the vascular lesions. For a detailed study of other histopathologic changes the reader is referred to the work of Klinge and Grzimek.²³

Subcutaneous nodules constitute one of the most highly characteristic features of rheumatic fever. In 1881 Barlow and Warner³² wrote: "Such nodules are in themselves indicative of rheumatism." Cheadle²⁹ stated that the nodules are "absolutely and solely rheumatic" having, so far as he can judge, "no other origin or connection." Osler³³ expressed the opinion that "their presence may be regarded as a positive indication of rheumatism." Hawthorne¹⁶ in 1900 wrote: "The eruption of fibrous tumors in the subcutaneous tissue . . . is a final and unequivocal proclamation in favor of rheumatism." Coombs³⁴ has recently stated that the subcutaneous nodule is the most "rheumatic" of all the manifestations of orthodox rheumatic infection. Finally, it has been shown in recent years that the nodules exhibit a highly characteristic histologic structure which is strikingly similar to that of the Aschoff body in the myocardium.

One of us has shown elsewhere that subcutaneous nodules, with a highly characteristic histologic structure, are frequently observed in rheumatoid arthritis.³⁵ Clinically and pathologically these nodules show a remarkable similarity to those which occur in rheumatic fever. Indeed, the evidence suggests that the nodules in the two conditions represent different phases of the same, fundamental, pathologic process and that such differences as do exist are differences of degree and not of kind. Nodules with a similar histologic appearance have not been described in any other disease. Therefore, as Hawthorne has stated, it is impossible to insist upon the appearance of subcutaneous nodules as a conclusive proof of rheumatic fever and, at the same time, to maintain that rheumatic fever and rheumatoid arthritis are not related diseases. Manifestly one or the other conclusion must be abandoned.

Reference has already been made to the occurrence of cardiac involvement in rheumatoid arthritis. Although of relatively rare occurrence this appears to be of the same nature as that which occurs in rheumatic fever. Unfortunately, it is rarely possible to examine the heart pathologically during the acute stages of rheumatoid arthritis. It is, therefore, impossible to express any final opinion as to the exact nature of the changes which take place. However, it is of considerable interest that vascular lesions similar to those which occur in rheumatic fever also occur in the vessels of the subcutaneous nodules in rheumatoid arthritis.³⁵

7. *Immunologic Findings.*—Although the etiology of rheumatic fever has not been finally established, a large body of circumstantial evidence has been brought forward by Coburn²⁸ and others indicating that infection by *Streptococcus hemolyticus* plays a rôle of great importance in the production of the disease. This evidence is, for the most part, based on clinical, bacteriologic and epidemiologic studies. In addition, an important immunologic observation has been made by Todd³⁶ and by Coburn and Pauli³⁷ to the effect that the antistreptolysin titer of the serum increases significantly during a rheumatic attack. This evidence suggests that the rheumatic process is initiated by infection with *Streptococcus hemolyticus*.

In rheumatoid arthritis there is comparatively little clinical, bacteriologic, or epidemiologic evidence suggesting that *Streptococcus hemolyticus* is concerned in the production of the disease. There is, however, considerable immunologic evidence of a suggestive nature, although of a different order from that which has been obtained in rheumatic fever. It has been shown that, in the majority of instances, the serums of rheumatoid arthritis patients agglutinate hemolytic streptococci in significantly high titers.³⁸ Agglutination reactions of a similar nature are not observed in any diseases other than those due to hemolytic streptococcal infection. It has furthermore been shown that precipitins for fractions of hemolytic streptococci can be demonstrated in those serums which possess high agglutinating properties.³⁹ These findings offer suggestive evidence in support of the conception that infection by *Streptococcus hemolyticus* plays a rôle in the production of the disease.

Finally, reference should be made to the fact that the immunologic evidence suggesting hemolytic streptococcal infection is of a different nature in the two diseases. In rheumatic fever the serums show an increased antistreptolysin content but do not contain agglutinins in significantly high titers. In rheumatoid arthritis serums, on the other hand, significant agglutinins are present but the antistreptolysin content is not elevated, except in early and active cases.

In the present state of knowledge it is difficult to evaluate the significance of these immunologic findings in the two diseases. It is possible that they may represent different responses to infection by the same agent but no final opinion may be expressed until the etiology of both diseases has been definitely established.

DISCUSSION

The relationship between rheumatic fever and rheumatoid arthritis is, at the present time, of greater theoretical than practical importance. For clinical

purposes it is important that the two should be differentiated whenever possible for, in typical cases, each presents its own symptoms, each demands its own therapeutic management and each requires its own prognosis. For theoretical reasons, however, a clearer understanding of the nature of the relationship of the two diseases is of great importance and may contribute much to our knowledge of both conditions.

Evidence has been presented to show that rheumatic fever and rheumatoid arthritis are intimately related and possibly different manifestations of the same pathologic process. Of particular significance is the clinical and anatomical evidence obtained from a study of "atypical" and "borderline" cases. The clinical evidence suggests that the two form a continuous sequence of one disease process with different expressions in each individual phase. These different expressions appear to be in large measure determined by the age of the patient but undoubtedly other factors, such as individual host susceptibility, are also of importance. The pathologic evidence, representing a difference in degree rather than in kind, strongly suggests that the two represent different responses to the same, or closely related, etiologic agents.

A final understanding of the relationship between rheumatic fever and rheumatoid arthritis will not be possible until the etiology of both diseases has been definitely established. At the present time there is a certain amount of evidence suggesting that infection by *Streptococcus hemolyticus* plays a rôle in the production of both diseases. However, this evidence is as yet far from complete and, even if it could be established that both diseases were due to the same agent, it would not prove their identity. The situation would then be analogous to that which exists with syphilis and yaws. Here the etiology of both diseases is definitely known, yet the relationship between the two is still a matter of controversy. It is obviously more difficult, with the knowledge at present available, to arrive at a complete understanding of the relationship between rheumatic fever and rheumatoid arthritis.

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DISCUSSION

DR. CURRIER MCEWEN, NEW YORK, N. Y.—A few years ago, at the suggestion of Dr. Swift, we studied supravitality the cells of rheumatic subcutaneous nodules, to obtain further information about the nature of the typical cells of rheumatic granulomas. The appearance of these cells when exposed to Janus green and neutral red was found to be different from that of cells of certain other granulomas. It seemed useful to conduct a similar study of the subcutaneous nodules of rheumatoid arthritis. In nodules from eight such cases we have been able to examine the living cells and have found them in all essentials the same as those of the subcutaneous nodules of rheumatic fever. Similar studies of granulation tissue removed from joints at operation showed the cells to have the same characteristics. This is in marked contrast to syphilitic and tuberculous granulation tissue. Thus it is seen that not only is the general microscopic appearance of the granulomas of rheumatic fever and rheumatoid arthritis similar, but also the individual cells of these lesions are the same. This does not by any means prove the identity of the two diseases, but it is one more link in the chain of evidence connecting the two.

DR. JOHN R. PAUL, NEW HAVEN, CONN.—Drs. Dawson and Tyson deserve credit for emphasizing with such vigor a relationship between these diseases. Many have hinted at their similarity, but few have insisted that they are both the same disease. It seems to be essentially a question of definition. As it is difficult or impossible to define rheumatic fever, it is equally difficult to insist that another disease picture actually is rheumatic fever.

Drs. Dawson and Tyson suggest that the difference between the two conditions is a question of virulence of the organism or of the susceptibility of the host. It seems to me that the susceptibility of the host should be considered first, in that there are certainly few diseases in which the symptomatology is conditioned by age more than it is in rheumatic fever, resembling tuberculosis in that respect. The presence of different types of cases of rheumatic fever and rheumatoid arthritis within the same family is perhaps an example of this age susceptibility. We recently saw a family in which a child of four years developed acute rheumatic carditis, a child of nine, subacute rheumatic fever with joint involvement, and just about the same time the mother developed rheumatoid arthritis.

It is one thing to admit that there is probably a relationship between these two conditions, but it is another thing to have to act upon the suggestion. We have had this decision brought to us very seriously in our work on the epidemiology of rheumatic fever

among families and communities. In certain communities we have been struck by the high incidence of rheumatic fever. We have also found a high incidence of cases of rheumatoid arthritis in these same communities. For our own practical purposes we have, in some instances, almost been forced to consider these two clinical pictures as manifestations of one disease.

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—Dr. Dawson has made a good case in favor of the relationship between rheumatic fever and rheumatoid arthritis. However, in following a number of cases of rheumatic fever over a period of years, I have never observed a single patient with rheumatic fever develop chronic arthritis. Many of my patients have reached the period between twenty and thirty years of age when they would be expected to develop rheumatoid arthritis. If these two diseases are closely related it seems to me that I should have observed an occasional case of rheumatic fever develop into rheumatoid arthritis. I have seen four instances when patients in the early teens have developed long-continued swelling about various joints which looked much like rheumatoid arthritis but in each instance the joints did finally clear up completely with no change therein as evidenced by x-ray examination. Those of us who are studying rheumatic fever from its inception should be able to answer this question if we live long enough.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—We have heard much about the age incidence in the development of these diseases, but have possibly neglected another important temporal factor, the period during which the patient may have been exposed to conditions, either infectious or environmental, favorable for the development of the particular type of rheumatism from which he may be suffering. This idea arises from an interesting observation of Dr. Boas a few years ago, that adult Porto Ricans who had recently come to New York from Porto Rico often had the type of rheumatic fever we are accustomed to see in children who have resided in New York all their lives. It is probable that the lack of rheumatic fever in Porto Rico has resulted in these people not developing any resistance to the disease, so that when they suffer their first attack their tissues are in a condition somewhat comparable to that of children.

DR. J. A. KEY, ST. LOUIS, MO.—It is interesting to study two diseases that are so different. I do not know much about rheumatic fever, but I do feel that it is quite dangerous to assume that two diseases are identical or closely related because similar nodules are present in each. Personally, it has been my impression that rheumatoid arthritis was not familial and that hypertrophic arthritis might be familial. I hope that Drs. Dawson and Tyson will continue their studies and later give us a paper on the differences between rheumatoid arthritis and rheumatic fever.

DR. R. L. CECIL, NEW YORK, N. Y.—Dr. Dawson's ideas are intriguing. It has occurred to me, however, that there is one stumblingblock in the way of accepting them, namely, the occurrence of Still's disease in children. If the differences between the two diseases are dependent largely on age, it would be hard to explain Still's disease, a condition now generally looked upon as rheumatoid arthritis in childhood.

DR. DAWSON (closing).—We appreciate that rheumatic fever and rheumatoid arthritis in their classical forms are distinct clinical entities, and we believe that it is important that they should be distinguished clinically. However, we do insist that the two disease pictures overlap and that it is frequently impossible to separate them.

We do not feel that the occurrence of Still's disease, which we regard simply as rheumatoid arthritis in children, constitutes a serious obstacle to our argument. After all, cases of Still's disease are relatively rare and these patients not infrequently show evidence of cardiac involvement, usually pericardial. On the other hand, one occasionally sees cases of orthodox rheumatic fever late in life; but, again, such cases are most unusual compared with the incidence in childhood.

Regarding the development of chronic joint changes following orthodox rheumatic infection, Dr. Shapiro does not encounter them because he is working exclusively with children.

We are dealing with an older group of patients and such cases not infrequently come to our notice. Furthermore, we feel that there may be a difference in the clinical picture of these two diseases in different parts of the world. For example, Freund in Vienna reports 110 cases of "secondary chronic polyarthritis" and Fischer in Germany reports 202 cases in his own personal experience.

A plausible explanation for the different conceptions held by different clinicians regarding the relationship of the two diseases may be found in the type of cases studied. We have primarily been interested in a large group of ambulatory patients. In our material borderline cases are encountered much more frequently than is generally supposed.

GEOGRAPHIC DISTRIBUTION OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN THE UNITED STATES

E. STERLING NICHOL, M.D., MIAMI, FLA.

WHEN it was suggested that a summary of our knowledge of the regional distribution of rheumatic fever and rheumatic heart disease in this country would be timely, I was reminded of a remark by Poynton under somewhat similar circumstances in England some years ago when he said, "I am in the position of one who has already overwritten himself on the subject (rheumatic fever), and we know that knowledge advances much more slowly than the writing of papers." So it is with apology for repetition that I have gathered together in review the data showing the variable geographic distribution of both rheumatic fever and rheumatic heart disease in the United States. It is hoped that the restatement of these surveys may stimulate others to appraise more accurately the incidence of this disease in their own regions. By way of emphasizing the influence of geographic location on the clinical incidence of rheumatic fever and rheumatic heart disease, my studies on this score in southern Florida are included.

Compilation of hospital statistics from various cities by Faulkner and White¹ and Harrison and Levine² in 1924 indicated that the incidence of rheumatic fever is much lower in the southern than in the northern part of the United States. In 1926, Wood, Jones and Kimbrough³ showed by comparative analysis of hospital records that rheumatic heart disease is half as common in Virginia as in Massachusetts. It was further shown by the collection of hospital data of Seegal and Seegal⁴ in 1927 that although the incidence of rheumatic fever anywhere varies with the years, yet for a given period of years the incidence in southern cities is markedly lower than in northern cities of this country. It should be noted that these authors, recognizing that data compiled from questionnaires filled out by hospital record clerks might be inaccurate, cautioned against too much reliance being placed on their rates.

Other studies of the incidence of rheumatic fever or rheumatic heart disease in various localities have been recorded and are included in Tables I and II. In considering this data it is necessary to keep in mind just what concept each author had regarding the inclusiveness of the term "rheumatic fever." In general the condition may be said to include cases with and without arthritis, rheumatic carditis whether acute, subacute or "smouldering," and chorea. Chronic, inactive cases of rheumatic heart disease were not usually classed as rheumatic fever. Any departure from this usage of the term will be noted in the tables, but two instances merit special comment. In 1931 Longcope⁵ in discussing the variations in the manifestations of rheumatic

fever in relation to climate, stated that in Baltimore the incidence of rheumatic fever admissions to adult medical wards of Johns Hopkins Hospital was 1.3 per cent which is equivalent to the rate given for a similar hospital in Boston. This is surprising until one discovers that Longcope counted cases of *quiescent* or *inactive* rheumatic heart disease as examples of rheumatic fever. The discrepancy becomes apparent on comparing the autopsy statistics given by the same author, which indicate that rheumatic heart disease is encountered at autopsy in Baltimore with less than half the frequency found in Boston. This author did emphasize, however, that the arthritic manifestations of rheumatic fever are less outspoken in that locality, compared with cities farther north, and that it is essentially a disease of the heart of a rather insidious type. Likewise in 1933, McLean⁶ in computing the admission rate

TABLE I

ADAPTED FROM PUBLISHED DATA REGARDING HOSPITAL INCIDENCE OF RHEUMATIC FEVER IN THE UNITED STATES

LOCATION OF HOSPITAL	LAT. N.°	YEARS INCLUDED	MED. ADM. RATE RH. FEVER OR CHOREA	REPORTED BY
Spokane, Wash.	47	1920-23	3.0	S. & S.†
Portland, Ore.	45	1920-25	1.2-4.5	S. & S.
Portland, Ore.	45	?	0.1*	Coffen ¹⁴
Boston	42	1914-23	1.85*	H. & L.
Boston	42	1918-22	1.3	F. & W.
Cleveland	41	1920-25	2.0-5.0	S. & S.
Iowa City	41	1923	2.4	F. & W.
Omaha	41	1923	0.7	F. & W.
New York	40	1915-25	2.0-6.0	S. & S.
New York	40	1915-31	0.1-1.8**	Davis ¹⁵
Philadelphia	39	1918-23	0.5-1.2	F. & W.
Baltimore	39	1914-22	0.7*	H. & L.
Baltimore	39	1925-30	1.3†	Longcope ⁵
Denver	39	1924-25	1.0-2.1	S. & S.
St. Louis	38	1922-23	0.47	F. & W.
St. Louis	38	1916-23	1.0*	H. & L.
University, Va.	38	1926-32	1.5†	H. W. & D.
San Francisco	37	1920-25	1.2-1.6	S. & S.
San Francisco	37	1919-23	3.75	F. & W.
Norfolk, Va.	36	1926-32	0.15	H. W. & D.
Oklahoma City	35	1922-25	0.0-0.2	S. & S.
Memphis	35	1920-25	0.1-0.5	S. & S.
Los Angeles	34	1921-24	0.44	F. & W.
Augusta, Ga.	33	1918-23	0.08	F. & W.
Birmingham	33	1917-25	0.0-0.5	S. & S.
Birmingham	33	1922-32	1.8†	McLean ⁶
San Diego	32	1925	0.45	S. & S.
Charleston	32	1923-25	0.1-0.2	S. & S.
Dallas	32	1919-25	0.0-0.3	S. & S.
New Orleans	29	1915-25	0.1-1.0	S. & S.
New Orleans	29	1916-23	0.3*	H. & L.
Galveston	29	1915-25	0.0-0.2	S. & S.
Galveston	29	1913-23	0.8*	H. & L.
Tampa	27	?	0.4	B. & C.
Miami	25	1930-34	0.13	Nichol‡

*Cases of chorea not included.

**Includes *only* cases with arthritis.

†Includes *also* chronic inactive rheumatic heart disease.

‡My own figures added for comparison.

‡S. & S., Seegal and Seegal⁴; H. & L., Harrison and Levine²; F. & W., Faulkner and White¹; H.W. & D., Hart, Wood and Daughton¹⁰; B. & C., Bitzer and Cooke¹⁷.

of rheumatic fever at the Children's Hospital in Birmingham included all instances of *chronic* or *inactive* rheumatic heart disease, with the result that the rate obtained of 1.8 per cent is considerably higher than it would be had the usual clinical concept been followed. There is no doubt, however, that the incidence of rheumatic fever in Birmingham is relatively high compared with some sections of the South, though unfortunately no autopsy statistics were given. McLean also showed the infrequency of arthritis as a manifestation of rheumatic fever in Birmingham and stressed that there, also, rheumatic fever is primarily a disease of the heart.

Another factor possibly detracting from the reliability of the comparative data in Tables I and II is the varying alertness of the attending physicians making the diagnosis of rheumatic fever in each instance, or judging whether a given case of heart disease is of rheumatic etiology. In children in particular it is commonly admitted that the early stage of heart disease is not an easy subject. The variable picture of the rheumatic state has been amply portrayed in clear fashion by Coburn,⁷ and in a recent monograph dealing with the etiology of rheumatic heart disease, Paul⁸ has stressed the difficulty of making accurate etiologic studies of a disease so variable in its presenting symptoms.

TABLE II

REPORTED FREQUENCY OF RHEUMATIC TYPE OF HEART DISEASE AMONG HOSPITALIZED
"CARDIAC" PATIENTS IN VARIOUS CITIES

HOSPITAL LOCATION	LAT. N.°	YEARS	% OF RHEUMATIC HEART DISEASE	REPORTED BY
Portland, Ore.	45	1929	10.1	Coffen ¹⁴
Boston	42	1924	39.8	Wood, et al. ³
Chicago	41	1932-33	16.7	Flaxman ¹⁸
Salt Lake City	40	1927-29	40.4	Viko ¹⁹
Louisville	38	1928-33	8.0	Simmons ²⁰
University, Va.	38	1923-26	21.9	Wood, et al.
Washington, D. C.	38	?	6.0	Gaeger and Dunn ²¹
Nashville	36	1930-31	10.5	Laws ²²
Galveston	29	1920-26	7.3	Stone and Vanzant ²³
Miami	25	1931-34	19.0*	Nichol

*Only 2 per cent was acquired in Florida. My own figures added for comparison.

In spite of these difficulties, after making allowance for the probable errors in the collected data and the difference in clinical concepts, it seems apparent on reviewing the data, that, on the whole, clinically perceptible rheumatic fever and rheumatic heart disease are much less common in southern than in northern regions of the United States. Nevertheless, a comparison of the frequency with which rheumatic heart disease is encountered at autopsy in various sections of the country obviously should give the most accurate index of the influence of geographic location and climate on the occurrence of rheumatic fever. Some of the autopsy data given by Harrison and Levine² and a few other reports of the incidence of rheumatic heart disease found at autopsy in certain regions have been combined in Table III. My own figures for southern Florida have been added for comparison. It is only fair to point out that in some southern cities autopsy statistics may give rise to an

exaggerated notion of the incidence of rheumatic fever, since the winter resort regions are invaded during the winter months by many individuals from the North with rheumatic heart disease, some of whom eventually die while in the South and make up a fair share of cases arriving at necropsy. It will be seen

TABLE III
REPORTED FREQUENCY OF RHEUMATIC HEART DISEASE FOUND AT AUTOPSY
IN VARIOUS CITIES

HOSPITAL LOCATION	LAT. N.°	YEARS	% OF RHEUMATIC HEART DISEASE	REPORTED BY
Boston	42	1914-23	4.0	Harrison and Levine ²
Cincinnati	39	1927-30	3.0	Glazer ²⁴
Baltimore	39	1925-30	1.6	Longcope ⁵
Oklahoma City	35	1919-24	0.0	Harrison and Levine
New Orleans	29	1916-24	0.2	Harrison and Levine
Miami	25	1931-34	4.0*	Nichol (present report)

*Actually only 0.5 per cent if allowance is made for migration of patients.

the available data indicate that the ratio of rheumatic heart disease found at autopsy in southern cities is much less than in northern cities. It has been suggested⁹ that since these studies are based on gross pathologic findings, such as the presence of mitral stenosis or rheumatic pericarditis, that further studies should be made including microscopic examination of standard sections of the heart tissues to make sure that some grades of rheumatic carditis have not been overlooked.

INCIDENCE IN SOUTHERN FLORIDA

A more striking portrayal of the way geographic location and climate influence the distribution of rheumatic fever and rheumatic heart disease in this country is seen on comparing my own studies in southern Florida (25° latitude N.) with the figures from Boston (43° latitude N.). Having made further inquiry since my previous reports¹⁰ on this subject, I have combined the data for the five-year period from 1930 to 1934 inclusive, showing the incidence of rheumatic fever and rheumatic heart disease at Jackson Memorial Hospital, Miami, an institution admitting patients of all descriptions. Previously published data for the years prior to 1930 are not included, as it is only since that date that practically all patients admitted to the hospital wards with rheumatic fever or rheumatic heart disease have been examined by the author. It is felt that this close acquaintanceship with the patients making up this data lends considerable weight to its importance, as all questionable instances of rheumatic infection were carefully studied in order properly to classify them.

During the five years there were only 11 cases of rheumatic fever or carditis, acute, subacute or "smouldering," and no cases of chorea, found among 8,287 medical admissions, including children, giving an admission rate of 0.13 per cent (Table IV). This is in sharp contrast to the admission rate during the same period at the Peter Bent Brigham Hospital, Boston, of 1.4 per

cent, as determined by Levine¹¹ who found 137 cases of rheumatic fever, chorea or carditis, acute or "smouldering," among 9,817 medical admissions. (The incidence would have very likely been even higher if children under twelve years were admitted to this hospital.)

TABLE IV

COMPARISON OF HOSPITAL MEDICAL ADMISSIONS FOR RHEUMATIC FEVER IN BOSTON AND MIAMI DURING 1930-34 INCLUSIVE

HOSPITAL	CITY	NO. MED. ADM.	NO. CASES RH. FEVER, RH. CARDITIS OR CHOREA
Peter Bent Brigham	Boston	9,817	137* or 1.4 %
Jackson Memorial	Miami	8,287	11† or 0.13%

*Twenty-three cases of chorea.

†No chorea; only 3 cases with arthritis.

TABLE V

INCIDENCE OF RHEUMATIC HEART DISEASE IN MIAMI AS DETERMINED FOR THE YEARS 1931-34 INCLUSIVE

NO. "CARDIAC" CASES OF ALL TYPES FROM		NO. CASES WITH RHEUM. HEART DISEASE	NO. CASES RHEUM. HEART DISEASE ACQUIRED WHILE IN MIAMI
Jackson M. Hosp.	561	106 or 19.0%	11 or 2.0%
Office practice	408	68 or 16.6%	2
Total	969	174 or 17.9%	13 or 1.3%

*Part of these cases are included in a previous communication.¹⁰

In view of this extremely low incidence of active rheumatic infection in Miami, it would be expected that in a series of cardiac patients hospitalized, the number classed as being of rheumatic origin would be correspondingly small. It is seen in Table V, however, that during the years from 1931 to 1934 inclusive there were 106 instances of rheumatic heart disease among 561 patients with cardiac disorders in the hospital. Although the percentage obtained (19.0 per cent) is only half that reported in some northern hospitals, it exceeds the ratio given for some northern points, as was seen in Table II. This discrepancy might indicate that many instances of *active* rheumatic carditis were overlooked in the hospital wards, but a study of the clinical histories of the patients classed as rheumatic heart disease reveals that *all* had acquired their structural cardiac damage before migrating South, except for those described above with *active* rheumatic infection. Thus only 2 per cent approximately of the total group of patients with heart disease should be classed as having rheumatic heart disease originating in Florida.

The frequency with which rheumatic heart disease is encountered in office practice in southern Florida is also illustrated in Table V. Of 408 cardiac patients examined in the period from 1931 to 1934 inclusive, 16.5 per cent or 68 were classed as being of rheumatic etiology, but with *one* exception all had acquired rheumatic disease before leaving the North, and *in only one* instance was there clinical evidence of reactivation of a "healed" rheumatic carditis among the 68 patients during their stay in the South. On combining the hospital and office data, it is seen that there were 174 instances of rheumatic heart disease among 969 cardiac patients (17.9 per cent). But only

13 patients or 1.3 per cent of the total group acquired rheumatic heart disease during their life or residence in Florida. In contrast to this, it has been shown by White and Jones¹² that in New England (Boston) among 3,000 patients with heart disease encountered in hospital, clinic, and private practice, 31.9 per cent were classed as being of rheumatic etiology.

On considering the available pathologic data, it was found that among 401 autopsies performed during the past four years at Jackson Memorial Hospital, there were 89 instances in which death was due primarily to heart disease, and of these 16 or 4 per cent gave anatomical evidence of *rheumatic* heart disease. But again on inspecting the clinical histories, it is shown that in fourteen instances the rheumatic pathologic changes had been noted in the North, and that in only two instances was the rheumatic infection acquired in the South. Thus, actually, only 0.5 per cent of the autopsies performed during this period showed rheumatic heart disease originating in Florida.

COMMENT

Many physicians have questioned the actual rareness of rheumatic fever in the South. As to the validity of their doubts for some sections of the South, I cannot vouch, but ten years of observation of the scene in southern Florida has convinced me that as far as this section of the South is concerned even the very mild or smouldering form of rheumatic carditis is quite uncommon while the obvious cases with arthritis or chorea are rare indeed. During the past five years in particular I have watched for the subclinical forms of rheumatic fever, which, it was claimed following my first report, probably escaped clinical notice. In my opinion there is very little ground for the feeling expressed editorially recently by Hench and others,¹³ that it might be better to have rheumatic fever in the North, where it is recognized early due to its more acute form, than in the southern states where the diagnosis might be missed, owing to an insidious onset, thus favoring more damage to the heart of the victim, who would go untreated for a longer period. If this were the case a general hospital in southern Florida should provide a far greater number of cases of rheumatic heart disease than it does, as seen above.

SUMMARY

A review of available data indicates that there is a definite inequality in the distribution of rheumatic fever and rheumatic heart disease in the United States, the amount being much less in the southern states. The influence of geographic location on the clinical incidence of rheumatic fever and rheumatic heart disease is emphasized by contrasting the findings in southern Florida and New England. During the past five years, in spite of a careful search for subclinical cases, the admission rate of rheumatic fever, rheumatic carditis or chorea in a general hospital in Miami was only one-tenth the rate in Boston during the same period.

Only 1.3 per cent of "cardiac" patients found in Miami both in hospital and office practice had rheumatic heart disease determined clinically to have been acquired during life or residence in the South, compared to a recent estimate that 31.9 per cent of "cardiac" patients encountered in New England were of rheumatic type.

This clinical evidence of a low incidence of rheumatic fever and rheumatic heart disease in the South is borne out to some extent by the available autopsy statistics, provided that in the figures for southern Florida allowance is made for the migration of patients from the North with previously established structural heart damage of rheumatic type. Further pathologic studies of a more detailed character are required to complete the proof of the influence of climate on the incidence of rheumatic fever.

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DISCUSSION

DR. JOHN R. MOTE, BOSTON, MASS.—This review of the geographic distribution of rheumatic fever in the United States is interesting and of importance not only in noting the incidence of heart disease in general, but also in a consideration of the possible etiology of rheumatic heart disease in particular. The hospital incidence of rheumatic fever or rheumatic heart disease may not indicate the real incidence of the disease in a given locality. This may be true especially in southern areas, where the disease in general is less obvious and less characteristic. In addition to the fact that the incidence of the disease decreases as you go south, medical men, according to their experience, differ in their concept of the disease and its significance, and this in itself may affect the apparent incidence. If the medical man believes it to be a trivial disease, the patient is considered well as soon as the joints are free from pain and is not sent to the hospital; whereas in the North, where the medical man may be more impressed with the importance of the illness, the patient may be hospitalized. Furthermore, the relative education of both local practitioners and of the general population in the use of hospitals will further affect the apparent incidence in different sections of the country. Not only may the above points affect the results in considering the incidence of this disease, but also the living conditions and social set-up in different sections and in different groups within a given section may alter the apparent incidence. Thus, White and Jones in the Massachusetts General Hospital wards found that 54 per cent of the cases with heart disease were rheumatic, while in office practice it was considerably less, and in consultation practice the incidence of rheumatic heart disease was relatively insignificant. It is obvious, therefore, that hospital records may not always indicate the real incidence of the disease.

That the incidence of the disease may vary in the same latitude is indicated by the report of Hart and Wood, who found an incidence of rheumatic fever at the University of Virginia Hospital in 1934 of 0.48 per cent of the total hospital admissions, while in the same year in the same latitude at Norfolk, Virginia, the incidence was 0.15 per cent of total admissions.

There are certain rank discrepancies in the reports from over the world on the occurrence of this disease which require verification. Clark states he has seen no rheumatic fever or mitral disease in the Malay States or in the British Army in Southern India, while Church reports a high incidence of rheumatic fever in Ceylon. Menje reported a high incidence in Tahiti, whereas in the Sansoon-Islands a very short distance away in the same latitude there is none. A verification of these and other discrepancies in the literature may throw a considerable amount of light on the possibilities in the etiology of this disease.

During the past five years the House of the Good Samaritan has sent each year a small group of children with rheumatic fever to the St. Francis Hospital in Miami Beach, Florida, in an attempt to evaluate, if possible, the effect of a subtropical climate on the course of the disease. During the first four years twenty-three children were sent. In summary of this study it may be said that recurrences with resulting death do occur in this climate, but in general the patients do better and their recrudescences are shorter lived than in the North. It should be stressed, however, that exacerbations of rheumatic fever do occur in rheumatic patients while they are in Florida.

DR. CURRIER McEWEN, NEW YORK, N. Y.—Assuming that the statement that rheumatic fever does improve in the tropics is correct, is the same true of atrophic arthritis?

DR. JOHN R. PAUL, NEW HAVEN, CONN.—I hope that we may soon begin to get some idea of the general prevalence of rheumatic fever in this country. I doubt if nation-wide data can be satisfactorily obtained from hospital admission lists, but a more satisfactory method is the determination of the prevalence of rheumatic heart disease among school children in different parts of the country.

DR. M. H. DAWSON, NEW YORK, N. Y.—While making rounds in a hospital in Jamaica, B.W.I., Dr. Dochez was shown a case or two recently of rheumatic fever. He remarked that he had understood that rheumatic fever was a very rare disease in the tropics. The attending physician replied, "Oh, no, we see cases from time to time, but there is a very curious thing about them, they all come from up in the hills," where, of course, the climate is not truly tropical.

DR. S. A. LEVINE, BOSTON, MASS.—I would like to comment on the difference in incidence of rheumatic fever in different parts of the country. Physicians down South may call rheumatic fever arthritis and so term it in their records. They say that we in the North see more rheumatic fever. In a large general hospital rheumatic heart disease must be seen if it exists in the community for it is eventually fatal. In a hospital of 200 beds in the course of ten years there will be a certain number of patients die of rheumatic mitral stenosis. At death it will be recognized by the pathologist, no matter what it was called in life. At the Charity Hospital in New Orleans the incidence of mitral stenosis was one-twentieth of that which we found at the Brigham Hospital in Boston. This was conclusive evidence to us that either rheumatic fever was markedly less common in New Orleans than it was in Boston or that rheumatic fever occurring down there does not affect the heart like it does in Boston.

DR. NICHOL (closing).—In reply to Dr. McEwen's question, I have no accurate data on the geographic incidence of atrophic arthritis. From an experience of ten years in southern Florida I would state that a patient with atrophic arthritis does not improve at the same rate that one with rheumatic heart disease does in the same period of time. I was asked to prepare some statistics regarding the incidence of atrophic arthritis, but I did not attempt to do so, because statistics not given from one's own experience have very little value.

No one should overlook Dr. Paul's excellent studies on school children. Three years ago I made a survey of the school children in Miami. The difficulties are almost insurmountable for a "one man job." On comparing 1,500 school children born and reared in Miami with 1,500 school children who had migrated to Miami I found that the incidence of rheumatic heart disease was four times greater in the "migrated" group than in the native group. However, some of those children had been sent to Florida because of a previously established rheumatic disease.

AN OUTLINE OF STUDIES RELATING TO VITAMIN C DEFICIENCY IN RHEUMATIC FEVER*

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IN PREVIOUS reports^{1, 2} experimental data have been presented indicating that under the combined influence of vitamin C deficiency and infection guinea pigs developed with considerable frequency, endocardial, myocardial, and articular lesions bearing considerable resemblance to those of rheumatic fever. On the basis of these observations, the concept was advanced that rheumatic fever may be the result of the combined influence of vitamin C deficiency and infection. Further experimental studies have confirmed and extended the original findings. It is the purpose of this communication to review the broad experimental basis for the concept, to consider certain epidemiologic and clinical data bearing on the problem, and finally to summarize the basic pathology of rheumatic fever and relate it to the thesis advanced.

EXPERIMENTAL METHODS

As detail of experimental methods has been previously published,^{1, 2} a brief outline will serve for the present communication. Guinea pigs were maintained on a basic diet containing all other food factors but devoid of vitamin C. In different experiments, varying grades of deficiency were maintained by regulating the vitamin C supplement which was given in the form of orange juice. The infecting agents in the majority of instances were hemolytic streptococci derived from spontaneous cervical lymphadenitis, which is a relatively common infection in guinea pigs. This use of natural pathogens for the species in all of the experiments is believed to be of considerable importance. It should be noted that there was definite variability in virulence of different strains of hemolytic streptococci used. The most striking lesions occurred in experiments where the virulence of the organism was great. Infection was transferred by intracutaneous inoculation of pure broth cultures of the organism. This resulted in a localized infection of the skin and regional lymph nodes. Occasionally but not commonly, metastatic abscesses occurred in distant sites. It should be pointed out that almost uniformly the local infection in the deficient animals was more intense, less well localized, and less readily healed, than in the control animals receiving adequate vitamin C supplements. While the most extensive observations have been made with the hemolytic streptococcus as the infecting agent and the most striking lesions have been observed with this organism, a few other bacteria including a gamma type streptococcus, *B. aertrycke*, and *B. bronchosepticus* have been used. Studies with these organisms have not been extensive; however, the occasional development of "rheumatic type" lesions, in which infection with these agents has been superimposed on the scorbutic state, suggests that the bacterial factor is not specific.

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An *active* or *virulent* infection would appear to be of more importance than the exact organism. This phase of the problem, however, requires further study.

EXPERIMENTAL FINDINGS

In each of a rather extensive series of experiments, the effects of the uncomplicated deficiency, the deficiency with superimposed infection, and the infection in the adequately nourished animal were studied. *The various infecting organisms in the presence of adequate nutrition, did not produce rheumatic type lesions.*

Inasmuch as the anatomic changes in the heart and articular tissues have previously been described and illustrated,^{1, 2} a brief review of the findings will suffice for the present communication. Subsequent studies have simply confirmed and extended the previous reports.

Heart Valves.—In uncomplicated vitamin C deficiency, atrophic and degenerative changes develop in the collagenous stroma of the heart valves. Rarely mild proliferative reactions accompany this degeneration. In vitamin C deficiency with superimposed infection, lesions of a combined degenerative and proliferative nature develop with considerable frequency. These lesions vary considerably and are sometimes striking in character and bear close resemblance to the early rheumatic endocarditis. Ribbert,³ Clawson,⁴ Poynton and Schlesinger,⁵ and others have clearly shown that the rheumatic vegetations develop within the valve substance, due to subendothelial proliferation of cells which is most prominent at the line of closure. Small amounts of true fibrin may merge with the cells in the superficial zone. This is essentially the nature of the experimental lesions as well.

Heart Muscle.—The pathologic changes in the heart muscle are less striking than the valvulitis. However, focal proliferative reactions are not infrequently observed. These may be found beneath the mural endocardium, in the pericardium and in the muscle. Some of the most significant reactions develop near the angle of attachment of the mitral valve. The reason, perhaps, that the lesions occur at this site is that there is here, as in the valve proper, a significant amount of intercellular substance (collagen) subject to undue stress and injury which forms the nidus for the proliferative focus. The connective tissue about the coronary vessel branches in the guinea pig heart is insignificant compared with that in the human heart.

The experimental proliferative foci, although not identical, are considered of a basically similar sort to the Aschoff reaction. The cells surround altered collagen and the nuclear and cytoplasmic character of the reacting cells correspond very closely to those composing the Aschoff body.

The Joints.—An early manifestation of vitamin C deficiency in the guinea pig is an arthropathy characterized by pain and swelling. Certain infections superadded to the deficiency accelerate and augment this arthropathy. The same infections in the presence of adequate nutrition do not affect the joints. Pathologic observations on the joints in rheumatic fever are not abundant. The most exhaustive study of the articular changes in rheumatic fever is afforded by the studies of Klinge,⁶ and Klinge and Grzimek.⁷ These authors find the lesions to be characterized by "fibrinoid" degeneration and granulom-

atous reactions in the capsular and periarticular tissues, mild hyperplasia of the synovial membrane with "fibrinoid" degeneration in the synovial and subsynovial tissues and the presence of hyaline fibrinous material free in the joint space. It is noteworthy that just such changes occur in the experimental animals.²

Much evidence has gradually accrued relating rheumatic fever and atrophic (rheumatoid) arthritis. Klinge and Grzimek⁷ hold that although acute or subacute rheumatic fever and atrophic (rheumatoid) arthritis may usually be differentiated, both disease pictures are so intimately related in both joint and general pathology that a "rheumatic" basis may be assigned to both. Dawson and Tyson⁸ have recently summarized a rather convincing mass of data indicating a relationship between the two diseases. It is perhaps not without significance that in the experimental studies under consideration, no sharp line can be drawn between a disease picture resembling rheumatic fever and one characterized by a chronic-deforming arthritis. Subacute or chronic vitamin C deficiency in the guinea pig produces a painful deforming arthropathy with manifold similarities to atrophic (rheumatoid) arthritis. These include synovial proliferation, intra-articular pannus formation and periarticular fibrous tissue overgrowth. In certain instances, superimposed infection accelerates and accentuates the pathologic process.⁹ The general atrophic changes found in atrophic (rheumatoid) arthritis involving the bony skeleton, muscle, and skin are also observed.

Subcutaneous Nodules.—One feature common to both rheumatic fever and atrophic (rheumatoid) arthritis is the subcutaneous rheumatic nodule. Dawson¹⁰ particularly has drawn attention to this lesion and finds the early pathologic histology in both conditions to be essentially the same. The lesion is characterized by hyaline streaks of fibrin surrounded by a reactive overgrowth of connective tissue cells. At times the fibrin is intimately intermingled with collagen. In the experimental animals, particularly those subjected to the more chronic deficiency, such nodules have been seen about joints with considerable frequency.

SUMMARY

It will be seen then that the concept that vitamin C deficiency may be a contributory factor in the etiology of rheumatic fever lies upon a broad experimental base. With vitamin C deficiency and infection combined lesions comparable to those of rheumatic fever are found not only in the heart valves and muscle, but also in the joints. Subcutaneous nodules serve to complete the pathologic similarity. No claim is made for the *identity* of the experimental lesions to those of the human disease. They are, however, thought to be *fundamentally similar*.

EPIDEMIOLOGIC CONSIDERATIONS

Malnutrition has commonly been observed in rheumatic fever. The geographic distribution, the dominant urban incidence, the high incidence in winter and spring and the frequent familial occurrence, might be explained upon the basis of greater liability to infection. On the other hand, these

features are entirely in accord with the operation of a factor of vitamin C deficiency. One epidemiologic peculiarity that particularly suggests an environmental factor other than infection in the genesis of rheumatic fever is the intimate relationship of the disease to poverty. Glover¹¹ believes that the true incidence of rheumatic fever in England is directly proportional to the degree of poverty and estimates that the occurrence of acute rheumatism is twenty or even thirty times as great in the poor as in the well-to-do. It would appear to me that a disease with such an amazingly high incidence in poor people could not be explained on the basis of a specific infecting factor or on the basis of recurrent nonspecific infection alone. Some fundamental environmental or nutritional influence would seem to lie in the background.

CLINICAL OBSERVATIONS

During the past eighteen months a clinical approach to the problem has been made in association with Dr. Amos Christie at the University of California Hospital. Dietary studies have indicated in most instances borderline or frankly deficient diets with respect to vitamin C particularly in the winter months. Capillary resistance tests have revealed in general low levels which have risen on institution of diets high in vitamin C. It is of interest that in many cases there has been a decided delay in return of this index toward normal indicating the necessity of time for repair of a vascular injury. We do not feel that a diminished capillary resistance is an entirely reliable index of latent scurvy and its reduction in rheumatic fever cannot be assigned to this factor alone. Excellent weight gains have been recorded. One mild recurrence occurred in a child who repeatedly informed us that she was unable to secure the foods advised. A number of the patients have passed through acute upper respiratory infections without reactivation of the rheumatic process. The patients in our series have not yet been subjected to detailed analysis, and we do not consider the group large enough or the period of observation long enough for conclusion. To date, however, we feel that the study has been encouraging. A recent observation of Faulkner¹² is of considerable interest. He found that rheumatic children showing evidence of active disease almost uniformly gave a reticulated red blood cell response of from 3 to 5 per cent following administration of large doses of vitamin C. To me this suggests a deficiency.

DISCUSSION

I wish to make it entirely clear that the factor of infection in rheumatic fever is in no sense minimized. It appears equally essential in the rheumatic fever-like experimental disease. What the precise infecting agent is, if there is a specific factor in rheumatic fever, is not known. It may be one or many forms of the streptococcus, an unknown bacterium, or a virus. Much evidence points to the importance of the common pathogenic hemolytic streptococci. The mode of action is equally uncertain. It may operate through toxin production, through minimal localization or through an allergic mechanism involving antigen antibody reactions. Epidemiologic data, particularly the social distribution, strongly suggests a conditioning environmental influence. The experimental data implicate vitamin C deficiency.

Essential Pathology of Rheumatic Fever.—Rheumatic fever is a disease fundamentally characterized by injury to connective tissues. Klinge⁶ particularly has drawn attention to widespread connective tissue injury. A change which he has called “fibrinoid degeneration” he considers to be the basic lesion of the disease. It seems to me that substances included in this descriptive term “fibrinoid degeneration” are one of the following: (1) Swollen, degenerated or necrotic collagen; (2) hyalinized fibrin; or (3) a combination of the two, that is, fibrin-soaked collagen. Collagen degeneration or necrosis is seen in the valvulitis, the auriculitis and at the center of the Aschoff body. Hyalinized fibrin may be present in any rheumatic lesion. It is usually most prominent in the subcutaneous nodules.

Theory of Mechanism.—A consideration of the fundamental pathology of rheumatic fever and the experimental studies suggest a possible mechanism, operating in the development of the lesions. Vitamin C has been shown by the studies of Höjer¹³ and Wolbach and Howe,¹⁴ to be essential for the normal metabolism of connective tissue. In the presence of deficiency, preexisting connective tissue substance undergoes degenerative changes and repair and replacement is either in abeyance or accomplished by an imperfect collagen. As the tensile strength of the finer vascular bed is dependent to a large extent upon the intercellular substances, collagen and reticulum, the deficiency would impair their strength and render them more permeable. If such tissues were further insulted by a factor of infection, it would not seem unlikely that they would suffer to a degree that would not occur in normal tissues. Such a concept would explain the acute necrosis or subacute degeneration of collagen, that is a fundamental lesion of rheumatic fever. The increased permeability of small vessels would foster this injury of collagen. If the insult of the infecting factor upon the small vessels were great, blood might escape into the perivascular connective tissues. This would explain the hemorrhagic manifestations commonly encountered in the disease. A lesser injury might allow only the escape of plasma from which fibrin would be deposited. The degenerated collagen, the fibrin or fibrin-soaked collagen would act as a stimulus to repair. The reparative mechanism in the presence of a deficiency and a continued action of the injurious factor of infection would be imperfect and manifest itself by pathologic hyperplasia of surrounding connective tissue cells as seen in the Aschoff reaction.

Existence of Latent Scurvy.—Considerable evidence has accumulated indicating that latent scurvy is probably more frequently present in children than is appreciated. Göthlin¹⁵ using reduced capillary strength as an index of latent scurvy found evidence of vitamin C undernutrition in 18 per cent of school children in the province of Uppland (Sweden) during the months of April and May. Dalldorf,¹⁶ working in New York, similarly using capillary resistance tests as a criterion considers that mild degrees of vitamin C deficiency may constitute a problem of considerable public health importance. If dietary histories can be relied upon, many of the rheumatic children in our series were on suboptimal diets, some frankly deficient in vitamin C. A recent survey of food purchases of families on relief in a California city¹⁷

revealed inadequate purchase of vitamin C containing foods in a large number of cases even though the survey was conducted in a season when these foods were plentiful and available at low prices.

Metabolism of Vitamin C.—The ability of the body to store vitamin C is limited. Even without a dietary source of the vitamin, there is a continued excretion of small amounts in the urine. Factors which may deplete the stores of vitamin C are of great interest and probably of great importance. Our own experience from experimental observations is that certain infections may act in this way. Harde and Benjamin¹⁸ have presented brief experimental evidence that infection may deplete the organic stores of vitamin C. Van Eekelen and Kooy¹⁹ have shown that fatigue may operate in a similar fashion. If acute infection depletes the organic store of vitamin C, it is of great importance to the concept presented. Under such circumstances, a mild degree of deficiency might by infection be rendered significantly severe in a relatively short period of time. Such a mechanism might afford a partial explanation of the latent phase noted by many observers between the acute upper respiratory infection and the clinical onset of rheumatic fever. Practically nothing is known of factors which may hinder or prevent absorption or utilization of vitamin C. In light of our limited knowledge of the metabolism of the vitamin interpretations based on studies of urinary excretion must be made with great caution. Harris and Ray²⁰ have shown that the normally nourished individual promptly excretes relatively large amounts of vitamin C following a large dose. On the other hand, deficient individuals show a lag in excretion. These observations are of considerable interest but conclusions based upon this type of study must be guarded. This method is obviously only a measure of immediate "saturation" level of the individual and gives no indication of a preexisting deficiency. Further, in the presence of a complicating factor as an infection it is probably not safe to assume that high excretion following test doses of vitamin C is an index of saturation. If infection may deplete the store of vitamin C, the ability of the body to utilize the vitamin may be disturbed.

What may we expect of vitamin C therapy in rheumatic fever? If vitamin C deficiency prepares the soil for an infection to produce the rheumatic injury, it is apparent that the deficiency then is only a contributory influence. If we consider the widespread and frequently severe character of this injury it will be appreciated that repair will require time. Further, it would seem that the reparative mechanism would probably be more or less ineffective during the active phase of injury. In severe cases it would appear that much of the finer vascular bed and connective tissues would need to be rebuilt and that these tissues would be susceptible to injury at any time until the restitution were complete. It will be seen then that we are dealing with something more complex than a simple deficiency. Time for repair would probably vary depending upon the extent and intensity of injury. Following severe cases, a period of months in which the tissues were liberally supplied with vitamin C and freed of injurious influences might be required for reestablishment of normal tissue anatomy and resistance. Naturally certain pathologies, as valvular deformities, would never be anatomically restored. The most that could be

achieved would be restoration of tissues to a state in which they could resist the injurious influence of infection. The ability of vitamin C to do this can only be evaluated on the basis of prolonged clinical observation.

Two approaches to the solution of this problem suggest themselves. First, a preventive type study to determine if optimal vitamin C nutrition over an adequate period of time will prevent susceptible groups from getting rheumatic fever. Likewise, a study of rheumatic children could be instituted to determine if a high vitamin C intake would materially reduce the tendency to recurrence. Particularly in this case should the element of time be carefully considered and judgment of effectiveness withheld until the period of observation had been long. The experimental and other data, which have been outlined clearly, indicate the importance of such a clinical study.

SUMMARY

The concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection, rests upon a broad experimental basis. In guinea pigs, under this dual influence, lesions comparable to those of rheumatic fever may develop in the heart and joints. The not infrequent occurrence of subcutaneous nodules appears to complete the pathologic similarity. It is of interest that in the experimental work no sharp line can be drawn between a disease picture resembling rheumatic fever and one characterized by a chronic joint disability with pathologic similarities to atrophic (rheumatoid) arthritis. There is much evidence indicating a relationship between the two diseases as seen in man.

Epidemiologic data seem to support the thesis advanced. Particular significance is attached to the abnormally high incidence of rheumatic fever in the poor.

Clinical studies in progress have afforded encouraging data, but are too few, and the period of observation too short to afford a basis for judgment.

Rheumatic fever is a disease fundamentally characterized by widespread injury to collagen. Based upon the experimental studies and pathologic anatomy of rheumatic fever, a theory of mechanism of the development of the rheumatic lesion is advanced.

Our knowledge of the metabolism of vitamin C is in the process of development. Capacity to store the vitamin is limited. Fatigue and certain infections may deplete the organic reserve. Factors which might inhibit absorption or utilization of vitamin C are not known. Urinary excretion studies may serve as an index of the immediate "saturation" level but are not a gauge of preexisting deficiency. The possible influence of infection in modifying the storage and excretion or utilization of vitamin C is not known. For these reasons, data based upon urinary excretion must be interpreted with care.

The question of what we may reasonably expect from vitamin C therapy in rheumatic fever is considered in the light of the fundamental pathology of the disease. Even though vitamin C deficiency may contribute to the development of the rheumatic lesion, it is only one factor. Some influence of infection also operates. In view of this, and the frequently severe injury

accompanying the disease, judgment of the preventive or therapeutic effectiveness of vitamin C administration in rheumatic fever can be based only on prolonged clinical study.

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DISCUSSION

DR. HOMER F. SWIFT, NEW YORK, N. Y.—Dr. Rinehart's report two years ago induced us to repeat it. The concept of synergic action of infection and some other factor is a useful hypothesis. Dr. Schultz, in our laboratory, has been able to confirm practically all of Dr. Rinehart's statements. One must ask, however, whether the experimentally induced lesions are truly rheumatic, or merely exaggerated scorbutic tissue changes. Thinking that the relationship between vitamin C deficiency and rheumatic fever would probably be revealed better in the clinic, Drs. Schultz and Sendroy have studied a group of patients in the Rockefeller Institute Hospital. Their results may be summarized as follows: No significant difference was found in the metabolism of vitamin C in rheumatic and non-rheumatic subjects. Fifty-seven previously rheumatic children were divided into two

groups; one received capsules containing 100 mg. of vitamin C daily in the form of Redoxon, the other a placebo. The relative incidence of mild rheumatic relapses among the patients in these two groups was the same; and three of the first group developed severe rheumatic relapses. Fifteen patients with acute active rheumatic symptoms were given 250 mg. of vitamin C daily without any observably favorable influence.

Although many of the rheumatic patients gave evidence of subnormal concentration of vitamin C at the time of admission to the hospital, others apparently had normal amounts in their bodies. Our clinical studies failed to prove the hypothesis that there was a causal connection between vitamin C deficiency and the symptoms of rheumatic fever. In view of the recently announced discovery of an antiinfectious vitamin in fruit juices, it is possible that studies with pure synthetic vitamin C might have given different results from those obtained by the use of citrous fruit juices.

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—During the past year I have carried on studies on possible vitamin C deficiency in rheumatic children. The criteria for a diagnosis of latent or subclinical scurvy are not at all clear. It is impossible to make such a diagnosis on patients on clinical findings alone. My work was carried out in the following manner: The habitual diets of 70 children who were known to have rheumatic fever, and of their families were investigated by a trained dietitian. Thirty-nine of these patients were on a diet which was sufficient in vitamin C content while 31 were on a diet which was definitely insufficient. The capillary resistance of these 70 patients was studied. A full mouth x-ray was taken, as well as an x-ray of a knee and a wrist. The capillary resistance test is not standardized and difficult to interpret. The various writers on this subject have used different methods for determining capillary resistance. Some have used simply the tourniquet for three minutes, others have used the blood pressure machine at 50 mm. for fifteen minutes and still others 80 mm. for three minutes while Dalldorf has used his so-called capillary resistometer which is based on negative pressure and takes only one minute to perform. These various methods were tried and an attempt made to correlate them. We decided to use Dalldorf's method because of its simplicity and reliability. It was noted that of the 39 children who had a sufficient diet 24 or 60.5 per cent had a positive capillary resistance test while 15 or 39.5 per cent were negative; and of the 31 children who were on an insufficient diet 19 or 61.3 per cent had a positive capillary test while 12 or 38.7 per cent had a negative test. This would indicate that there is no correlation, whatsoever, between the capillary resistance test and the deficiency of vitamin C in the diet. The factor of toxicity in these rheumatic children as a cause of the capillary permeability must be considered. One is unable to say whether or not the decrease in capillary resistance is due to toxicity or vitamin C deficiency. This preliminary report would indicate that capillary resistance and vitamin C deficiency are not definitely related.

We based our findings in the teeth on the work done by Westin and Höjer of Sweden. I was unable to show any relationship between vitamin C deficiency as indicated in the study of the diet and the findings in the teeth. Of 39 children on a sufficient diet 15 or 39.5 per cent were positive while 23 or 60.5 per cent were negative for dental changes. Of 31 children on an insufficient diet 12 or 40 per cent had positive findings in the teeth while 18 or 60 per cent had negative findings. In no instances did roentgenograms of the joints show definite evidence of latent scurvy. One meets with considerable difficulty as the roentgen findings in subclinical scurvy are not clear. We did find some unusual changes in the bones in a number of these children but consultation with Dr. Leo Rigler, the head of the x-ray department of our university, failed to establish a diagnosis of scurvy. Some of these films were sent to Dr. Bromer of Philadelphia and he also refused to commit himself on these findings. My preliminary investigations thus suggest that there is no relationship between vitamin C deficiency and juvenile rheumatism.

DR. WILLIAM J. KERR, SAN FRANCISCO, CALIF.—The work of Dr. Rinehart and the original work with Drs. Mettier and Connor have been of great interest. The histologic findings resemble closely those seen in rheumatic fever, and perhaps those in the proliferative type of arthritis. It is not so easy to carry results over to the clinic and say that

deficiency of vitamin C is a factor in the production of rheumatism or that we can immediately control the process by substituting vitamin C.

The work which Dr. Swift and his associates reported last month seems to be quite negative so far as the clinical application of the principle is concerned. But we should be sure that we have studied an adequate number of cases over a period of years before we can be quite certain of the results. We must also be sure that whatever substances we are administering actually enter the body. If these substances are given by mouth, conditions for their proper absorption must be satisfied. If there is any uncertainty about absorption we should give them parenterally. As I recall Dr. Swift's report, vitamin C was given intravenously in some instances. If there are other substances in fruit juices, which may be important factors, we should take them into account in treatment.

Dr. Rinehart and his clinical colleagues expect to continue this study for some time, not only on patients with rheumatic fever but also on those with atrophic arthritis.

DR. JOHN R. MOTE, BOSTON, MASS.—At the House of the Good Samaritan we repeated with minor variations the work of Dr. Rinehart on guinea pigs. Briefly it may be said that the results were essentially the same as those of Dr. Rinehart. The animals which had scurvy with an added streptococcus infection showed the most marked lesions in most instances. In the chronic scurvy controls we found the same type of lesion but of a less severe type. In the group of acute severe scurvy controls we found lesions of the type of the scurvy plus infection, which in most instances were not so severe, but in some just as widespread and severe as in the experimental group.

We have not been convinced that the lesions are either identical or even closely similar to those of rheumatic fever.

DR. J. A. KEY, ST. LOUIS, MO.—About fifteen years ago Dr. Howe produced arthritic changes in the joints of animals by diet. Dr. Wolbach found the changes represented atypical scurvy. I have studied guinea pigs on a mild scorbutic diet. Some of them developed changes in joints; first a shedding of the synovial lining cells. I wonder about Dr. Rinehart's controls and whether a similar series of animals kept on the same diet would develop the joint changes without injections of streptococci. In my own experience when streptococci are injected into animals they either develop a purulent arthritis or the joints are unaffected. I have not produced therewith a condition resembling chronic atrophic arthritis, and I do not believe that any guinea pig, rabbit, or other laboratory animal ever develops rheumatic fever or atrophic arthritis. So where are we going to get animal streptococci to produce these diseases in animals?

DR. WALTER BAUER, BOSTON, MASS.—If a lack of vitamin C plays a rôle in the causation of rheumatic fever, why is the incidence of rheumatic fever no higher in infants suffering from scurvy?

I am very doubtful that vitamin C deficiency plays any important rôle in the production of atrophic arthritis for the following reasons: For the past five years each patient discharged from our hospital with the diagnosis of atrophic arthritis has been instructed to adhere to a high vitamin diet so far as his pocketbook will allow. The dietary calls for one eight-ounce glass of orange juice each day and one eight-ounce glass of tomato juice each day. Many of these patients have adhered to this diet for from three to five years, yet the results in this group are no different than in the group who did not adhere to the diet. If what Dr. Rinehart says is true, one would expect to see a difference in the therapeutic results in these two groups.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—Investigators studying artificial inoculation of laboratory animals with streptococci should understand the advantages to be derived from a knowledge of the serologic groups to which the particular strains they are using belong. Members of groups which are spontaneously pathogenic for man are generally not spontaneously pathogenic for animals, and groups pathogenic for animals have little disease inducing capacity for man. A common source of error is that we use so-called "human strains" to inoculate laboratory animals and expect these animals to have the same reactions as man. This was doubtless done in the experiments mentioned by Dr. Key;

but in Dr. Rinehart's work a group C strain was employed, a strain that is normally pathogenic for guinea pigs, and one that satisfactorily induces chronic lesions in these animals. This is a good example of using the proper experimental agents in conducting experimental studies.

DR. ERNEST E. IRONS, CHICAGO, ILL.—Some years ago we were studying chronic arthritis in hogs from which two organisms were isolated, a streptococcus and a short bacillus described in veterinary medicine. We inoculated a litter of little pigs with these organisms and had no trouble in producing chronic arthritis with persistent large articular deformities. In other laboratory animals no arthritis resulted from inoculations. As Dr. Swift stated, to get characteristic lesions in animals the organism used must be suited to the animal inoculated. To me this has always seemed to be one of the weak spots in animal experiments in respect to human disease.

DR. RINEHART (closing).—The studies of Dr. Wolbach referred to by Dr. Key have shown that vitamin C is essential for the normal metabolism of connective tissue and the formation of normal intercellular substances. His experiments were designed to demonstrate this fact, and dealt essentially with acute deficiency and the early reparative process following administration of the vitamin. His experiments therefore differ materially from those which I have reported. We have controlled all of our work, in studying the effect of deficiency alone, the deficiency combined with infection, and the infection in the presence of adequate nutrition. The guinea pig subjected to subacute or chronic vitamin C deficiency alone develops a chronic arthritis with many similarities to atrophic arthritis. It is probable that Dr. Howe's animals presented comparable changes. In this sense, the pathologic picture is truly that of scurvy but differs radically from the usual concept of the disease. The rôle of infection is of interest. If a factor of infection is added to the deficiency, the arthritis may be accelerated in development, and aggravated in intensity. This is not uniformly so, depending apparently on the type and virulence of the organism used. On the other hand, the various infecting agents alone in the presence of an adequate vitamin C, did not produce arthritis or other rheumatic manifestations.

I am glad that Dr. Swift and Dr. Irons emphasized the importance of using organisms from animal sources in animal experimentation. In our studies we used almost exclusively organisms derived from spontaneous guinea pig infections. I think this is one reason why Dr. Mote's studies have not been in accord with our own. Some of his experiments were made with organisms from other sources. In our own work a factor of infection in addition to the vitamin C deficiency appears essential for the production of the experimental picture resembling rheumatic fever. Even in using organisms that are naturally pathogenic for the species, we have found that they vary considerably in effectiveness.

Dr. Swift notes that our experimental findings have been essentially confirmed in his laboratory. On the basis of studies of storage and excretion of vitamin C and on clinical therapeutic studies, he concludes that "we have no real evidence that vitamin C is an important determining factor in the etiology of rheumatic fever." It must be noted that our knowledge of the metabolism of vitamin C is incomplete particularly when complicated by a factor of infection. Under such circumstances excretion of vitamin C in the urine may not denote saturation. It may be an expression of depletion or an inability to utilize the vitamin. Does the rheumatic process, once initiated, impair the absorption or utilization of vitamin C? In pernicious anemia certain infections impair the utilization of liver extract, necessitating great increases for an effective dose. Even though we could be assured that excretion of vitamin C implied saturation of tissues, this would give us no index of a past episode of deficiency as a basic contributory factor. With respect to a lack of immediately measurable improvement following the administration of large amounts of vitamin C, in cases of rheumatic fever, it would seem unlikely that saturation of the body with the vitamin would quickly restore a tissue change that has been acquired over a period of years or has resulted from repeated insult. A widespread and frequently severe connective tissue and vascular injury is found in rheumatic fever. The exact mechanism of this injury is unknown. Even though vitamin C deficiency may be a factor in the initial mechanism, another influence, probably infection, also operates. If this injury can be

repaired by vitamin C, time would appear essential. I wish strongly to emphasize the importance of this in the evaluation of clinical protective or therapeutic studies. In severe cases it would appear that much of the finer vascular bed and its connective tissue support would need to be reconstructed and this repair could probably start effectively only after cessation of the injury.

Dr. Shapiro has questioned the value or meaning of capillary resistance tests. We are aware of the limitations of this test as an index of latent scurvy. However, repeated observations over long periods of time indicate its significance. The capillary strength in general is reduced in rheumatic fever. Although the levels of capillary strength rose on administration of generous amounts of vitamin C, in many cases this return toward normal levels required several months, indicating a delayed restitution of tissue injury.

Dr. Bauer notes that his patients with arthritis have, on discharge, been instructed to take generous amounts of vitamin C and does not feel that improvement in this group is significantly different than other groups. Most diets recommended in arthritis contain liberal sources of vitamin C. We only suggest that subacute or chronic vitamin C deficiency may be *one* mechanism or a contributory factor in the development of atrophic arthritis. In some cases we may have to look for abnormalities in assimilation or utilization of vitamin C. The profound circulatory and other anatomic changes which characterize the disease in its subacute or chronic stage, even though vitamin C lack had contributed to their development, would be slow to respond to the administration of the vitamin. A prolonged clinical study of this phase of the problem is needed. Dr. Bauer also asks why the incidence of rheumatic fever is not high in scurvy. I do not know of any analysis of scorbutic cases from this standpoint. Clearly recognizable scurvy in this country is almost limited to infancy. It is not improbable that a childhood deficiency, perhaps more chronic and less intense, but just as real, would not be recognized by our usual standards.

In conclusion, I wish to reaffirm the broad experimental basis for the concept presented and to stress the necessity for a prolonged clinical study as the basis for final judgment.

INFLUENCE OF THE TONSILS ON RHEUMATIC INFECTION IN CHILDREN

ALBERT D. KAISER, M.D., ROCHESTER, N. Y.

RHEUMATIC disease with its various manifestations has been clinically associated with tonsil infections for a considerable period of time. Extensive literature on this subject has appeared, which has not been in entire agreement. Tonsillectomy in selected children seemed to be followed by the subsidence of rheumatic manifestations and consequently this method of treatment was heralded as most successful. Such treatment was generally instituted until its practice became almost universal. However the good results seen in selected children were not always apparent when tonsillectomy was more commonly performed, so that the pendulum has gradually swung to the other extreme questioning whether tonsillectomy ever has any value in the treatment or in the prevention of rheumatic disease.

A review of the literature on the influence of tonsillectomy in rheumatic infection leaves one in doubt as to the exact relationship of the tonsils to rheumatic disease. There seems to be agreement on the observation that infection in the tonsils frequently precedes one of the rheumatic manifestations. On the other hand, many children subject to attacks of tonsillitis or sore throat do not develop evidences of rheumatic disease.

Assuming that infection in the tonsils occurs frequently in children who develop rheumatic disease, three questions naturally arise. First, Can the incidence of rheumatic infection in children be reduced if the tonsils are removed before rheumatic infection sets in? Second, Does tonsillectomy influence the course of rheumatic infection when the disease is once established? In other words, are there fewer recurrences of the disease? Third, Does the presence or the absence of the tonsils influence the outcome of this disease, or, stated otherwise, is the death rate increased or diminished by the treatment of the tonsils? If a satisfactory answer could be found for these three queries, it would be possible to state something definite about the influence that the tonsils exert on this disease.

In order to answer the first question on the incidence of rheumatic infection in children whose tonsils have been removed and in those whose tonsils have not been removed one must have information on a large group of children over a considerable period of time. A number of years ago a survey was undertaken in Rochester to obtain information on the general incidence of rheumatic manifestations in all of the school children. This information was obtained from the parents of the children. The parents of 48,000 children were interviewed. Of this number, 20,000 children had been tonsillectomized and 28,000

had not had their tonsils removed. The information obtained in this survey stated the number of children who at some time during their life had clinical evidence of rheumatic infection. It was impossible, however, to determine whether the first rheumatic manifestation preceded the tonsillectomy, if done, or whether it occurred after the tonsils were removed. It did nevertheless give a general idea of the incidence of the various rheumatic manifestations in children.

Based on these data as obtained from the parents nearly all of the rheumatic manifestations occurred less commonly among tonsillectomized children. Rheumatic fever which is usually a severe type of rheumatic infection was reported with considerably less frequency in the tonsillectomized children. Among the children with their tonsils out there were 37 per cent fewer cases of rheumatic fever. Muscular rheumatism, termed growing pains, was reported only slightly less often in tonsillectomized children. Chorea was noted with equal frequency

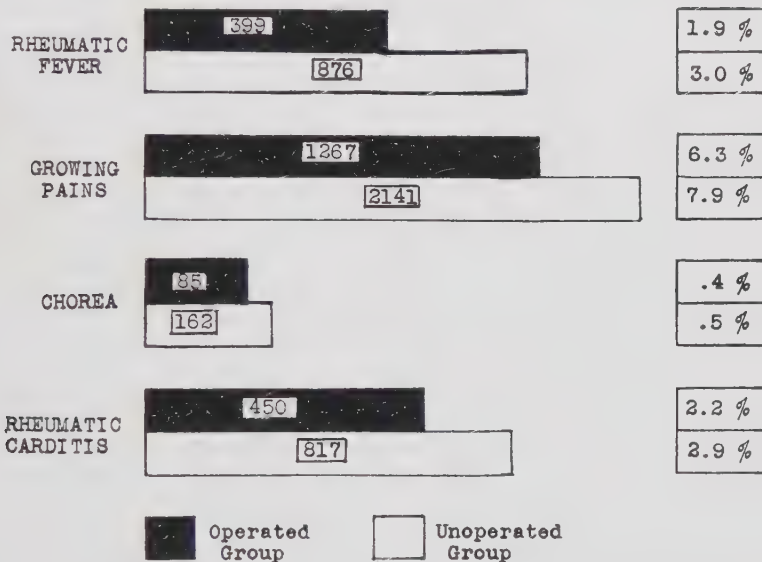


Fig. 1.—Chart showing comparative incidence of rheumatic manifestations in children on whom tonsillectomy has and has not been performed (based on the history of 48,000 school children of whom 20,000 had undergone tonsillectomy and 28,000 had not).

in the two groups while rheumatic carditis was somewhat less common among the children with their tonsils out. In this survey many children among the tonsillectomized group reported some rheumatic manifestation. In some of them the rheumatic infection began before the tonsils were removed. If it had been known whether the tonsillectomy preceded the rheumatic infection or followed it, a more favorable comparison for the operated group might be noted. This statistical information based on the parents' history of the child leaves some uncertainty in the value of the data. It does, however, clearly indicate that rheumatic disease occurs in children whose tonsils have been removed, and it also seems highly probable, as noted in Fig. 1, that initial attacks of rheumatic infection are somewhat less likely to develop in children whose tonsils have been removed.

More accurate information dealing with the initial infection and the presence or absence of tonsils was obtained from an analysis of 439 children with acute rheumatic infection who were observed over a five-year period from January, 1925, to January, 1930. Familiar with the number of children whose tonsils have been removed at various ages, it was possible to compute the expected incidence of rheumatic disease among tonsillectomized children in the community.

TABLE I

COMPARISON OF THE ACTUAL WITH THE EXPECTED RATE IN TONSILLECTOMIZED CHILDREN AMONG 439 CASES OF ACUTE RHEUMATISM

AGE OF CHILDREN	TOTAL NO. CASES	EXPECTED NUMBER OF RHEUMATISM CASES WITH TONSILS REMOVED	ACTUAL NUMBER OF RHEUMATISM CASES WITH TONSILS REMOVED	NUMBER OF RHEUMATISM CASES THAT DEVELOPED BEFORE TONSILLECTOMY	PER CENT OF ROCHESTER CHILDREN WITH TONSILS OUT
Under 5 years	38	3.8	2	36	10
5-10 yr.	126	42.0	22	104	33
10-15 yr.	239	119.5	88	151	50
16-17 yr.	36	19.8	11	25	55
Total	439	185—42%	123—28%	316	

For all ages, as noted in Table I, the actual number of children who developed rheumatism after the tonsils were removed, was considerably less than the expected rate. The difference between the percentage of those actually operated upon and the expected percentage operated upon is 14 per cent. Utilizing an accepted formula for determining the standard error of difference, it develops that the difference, 14 per cent, is statistically significant. About one-third more children figured on a percentage basis developed their first attack of rheumatism when the tonsils were in than those who had been tonsillectomized. The full value of removing the tonsils in the control of rheumatic disease in children cannot be ascertained from the study of rheumatic children only, as has been done by various authors. If tonsillectomized children from the same homes, schools and cities over the same period of time and of similar ages show fewer cases of rheumatism than a like group untreated, there is justification in believing that early enucleation of the tonsils has protected some children against this infection. Such has been the case in large groups of controlled children in Rochester.

Additional information was obtained on the significance of the tonsils in the prevention of the various rheumatic manifestations from a study of 4,400 children. Composed of two equal groups, tonsillectomized and nontonsillectomized, the various rheumatic manifestations could be compared inasmuch as these children were observed for a period of ten years.

As noted in Fig. 2 chorea was known to have existed in 7 of the 2,200 children who were subsequently tonsillectomized. An equal number of children with chorea were found in the group of 2,200 children who were not later tonsillectomized. During the ten-year period following tonsil removal, 26 children developed chorea, while among the 2,200 children not tonsillectomized, 13 developed chorea. The seriousness of chorea can be judged by the occurrence of carditis associated with chorea. The incidence of carditis in the children who developed chorea

while the tonsils were in was 62 per cent. Among the children who developed chorea after the tonsils were removed, the incidence of carditis was 47 per cent. The inference is that chorea is not influenced favorably with removal of the tonsils, except in safeguarding slightly against the serious complication of rheumatic carditis.

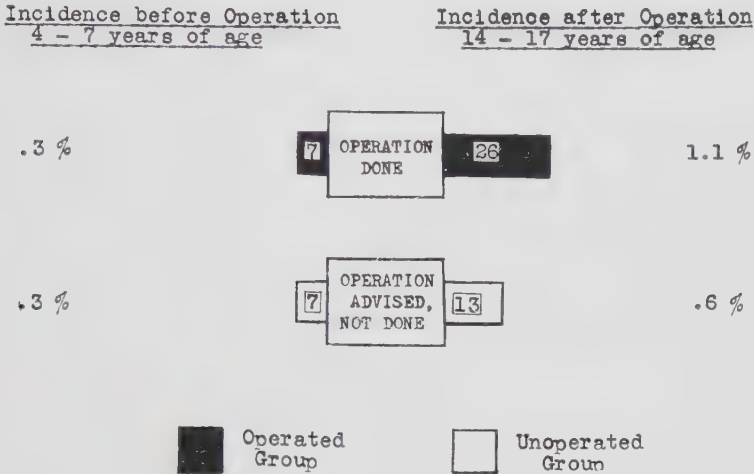


Fig. 2.—Incidence of chorea in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

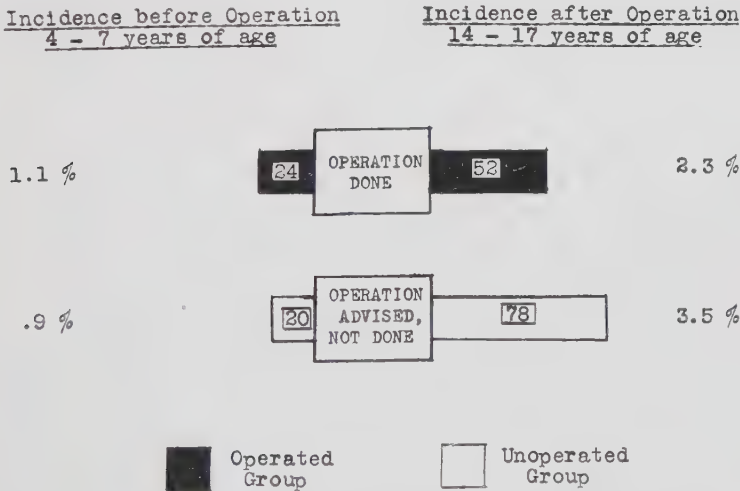


Fig. 3.—Incidence of rheumatic fever in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

The incidence of rheumatic fever was studied in the same two groups as shown in Fig. 3. Before removal of the tonsils 24 or 1.1 per cent of the 2,200 children had been afflicted with rheumatic fever, while among the control children, 20 or 0.9 per cent were similarly affected. During the ten-year period following tonsillectomy, 52 children or 2.3 per cent developed rheumatic fever, while 78 or 3.5 per cent of the control children were likewise infected. Realizing

that rheumatic fever occurs more commonly between five and ten years of age than before the fifth year, there is reason to believe that in this series, enucleation of the tonsils was responsible for about one-third fewer cases of rheumatic fever than in a similar group whose tonsils and adenoids were not removed. As with chorea, the occurrence of rheumatic carditis was studied. In the children who developed rheumatic fever for the first time after tonsil removal, 69 per cent developed rheumatic carditis. From this study it seems reasonable to conclude that removal of the tonsils offers some hope of escape from rheumatic fever. It occurred from 25 to 35 per cent less often in tonsillectomized children. The serious complication of rheumatic carditis is as likely to develop in children with rheumatic fever whose tonsils are out as in those whose tonsils are still present.

Though there is some doubt as to the relationship of so-called growing pains or muscular pains to rheumatism, it is now generally conceded that growing pains are mild manifestations of rheumatic infection. The incidence of this complaint

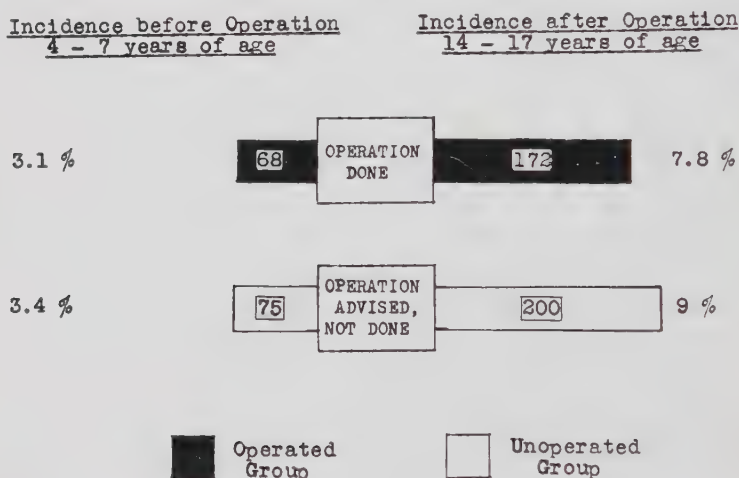


Fig. 4.—Incidence of growing pains or muscular pains in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

with reference to the tonsils has been studied in the 4,400 children. Muscular pains as shown in Fig. 4, interpreted as rheumatic pains, occurred with equal frequency in the operated and unoperated group before the sixth year of age. During the school age period, 172 tonsillectomized children, or 7.8 per cent, were subject to this complaint, while 200, or 9 per cent, of the nontonsillectomized children were having growing pains. The less serious nature of this complaint is recognized in the infrequent complication of carditis. Evidence of carditis was detected in 16 per cent of the children subject to muscular pains in whom the tonsils had not been removed and in 18 per cent of the children whose growing pains manifested themselves for the first time after the tonsils were removed. The milder manifestations of rheumatism known as growing pains or muscular pains seem to be less influenced by the absence of tonsils than is rheumatic fever. It occurs somewhat less frequently in tonsillectomized children, but carditis is as likely to follow this mild rheumatic infection after the tonsils are removed.

Rheumatic carditis was studied in the 4,400 children similarly to the other rheumatic manifestations. During the ten-year period in which these children were observed, it developed that 1.1 per cent of the children contracted rheumatic carditis following tonsillectomy, while among the children whose tonsils were not removed, 1.3 per cent contracted rheumatic carditis. The difference is not significant. If one judges the value of tonsil enucleation to children who have had an attack of rheumatic fever, there is little to commend the operation for the control of rheumatic carditis. If, however, one analyzes a large child population where the incidence of rheumatic fever and chorea is known, it is evident that slightly less carditis exists in tonsillectomized children. This lessened incidence is due to fewer cases of rheumatic fever among tonsillectomized children, and a somewhat diminished incidence of carditis following chorea in tonsillectomized children. These three separate studies justify the statement that the tonsils have

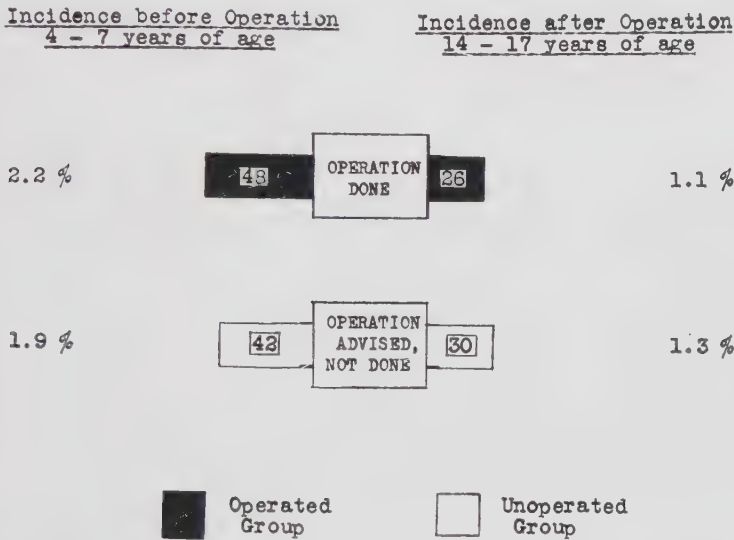


Fig. 5.—Incidence of rheumatic carditis in 2,200 children before tonsillectomy and ten years after operation as compared with an equal number of controls.

some influence on the incidence of rheumatic disease as recognized in children. They agree that rheumatic fever occurs about 30 per cent less often in children whose tonsils have been removed; that chorea occurs as often in tonsillectomized children as in those not so treated; that muscular rheumatism occurs slightly less often in the tonsillectomized children; that rheumatic carditis is found less often in the children whose tonsils have been removed.

In answer to the second query, Can recurrent attacks be influenced by tonsillectomy?—adequate data are available from several sources. Wilson, Lingg and Croxford prepared an excellent study of 413 rheumatic children in 1928 to determine the influence of the tonsils on recurrent attacks. In their survey, a careful correlation was made between the age of tonsillectomy and the age at which recurrent attacks occurred. It was brought out that recurrences occur in young children under nine years of age whether tonsils are removed or not while after ten years of age, recurrences are less common in both groups. Because of

their results they conclude that the routine removal of tonsils for the prevention of rheumatic heart disease in children is not justified by conclusive data. Poynton, on the other hand, believes that enucleation of the tonsils tends to stop severe recurrent throat infections, which on each occasion lay the rheumatic patient open to a recrudescence of the disease. In a study made by the author on 439 children who had acute rheumatism, the benefits of tonsillectomy in the prevention of recurrent attacks were not apparent.

TABLE II

INCIDENCE OF RECURRENT ATTACKS OF ACUTE RHEUMATISM WITH REFERENCE TO REMOVAL OF THE TONSILS IN 439 CHILDREN

AGE OF CHILDREN AT FIRST ATTACK	NUMBER IN WHOM FIRST ATTACK DEVELOPED BEFORE TONSILLECTOMY	NUMBER WHO HAD RECURRENT ATTACKS	NUMBER IN WHOM FIRST ATTACK DEVELOPED AFTER TONSILLECTOMY	NUMBER WHO HAD RECURRENT ATTACKS
Under 5 yr.	36	11—31%	2	1—50%
From 5 to 10 yr.	104	42—41%	22	10—45%
From 10 to 15 yr.	151	30—33%	88	19—21%
16 and 17 yr.	25	8—32%	11	4—36%

Recurrent attacks of rheumatism occurred as frequently in tonsillectomized children as in the untreated ones at all ages, except between the ages of ten and fifteen, when recurrent attacks are less common in both groups. The figures noted in Table II do not describe the seriousness of recurrent attacks, but in a general way, agree with the results obtained in Wilson's study. Though the number of recurrences of such manifestations as rheumatic fever, chorea, and muscular pains was not lessened by removal of the tonsils, it was demonstrated that carditis associated with recurrent attacks of rheumatic fever and chorea was somewhat less severe in the tonsillectomized children.

A solution was sought for the third question, Does the presence of tonsils in the rheumatic child influence the outcome of the infection? In a recent study made in Rochester the outcome in 597 rheumatic children was observed. In almost comparable groups the mortality rate was 13 per cent among the children whose tonsils were in during their rheumatic infection and 7 per cent among those whose tonsils were out at the time of the initial attack. This result suggests that the most serious type of rheumatic infection is more likely to occur in children whose tonsils are still present.

Though the removal of the tonsils fails to decrease the number of recurrences of rheumatic infections, there is a decidedly lower mortality rate among those

TABLE III

THE EFFECT OF THE TONSILS ON THE OUTCOME OF RHEUMATIC INFECTION IN 597 CHILDREN

TONSILS	NUMBER	DIED	ONE OR MORE RECURRENCES	NO RECURRENCES
Remained in	156	13%	46%	41%
Out at initial attack	187	7%	48%	45%
Out after initial attack	254	4%	44%	52%

children whose tonsils have been removed. If other studies show similar results, there is a definite indication in every rheumatic child for the removal of the tonsils.

There is statistical evidence based on controlled studies to justify the statement that tonsillectomized children are somewhat less likely to develop rheumatic manifestations. The lessened incidence of rheumatic infection is noted in cases of rheumatic fever and rheumatic carditis. Muscular rheumatism and chorea are as likely to occur in children whose tonsils have been removed as in those whose tonsils are still present.

The incidence of recurrent attacks of rheumatic manifestations is not influenced by tonsillectomy. If rheumatic disease occurs in children whose tonsils have been removed prior to the initial attack the number of recurrences is likely to be as great as in children whose initial rheumatic infection developed while the tonsils were still in. Where tonsillectomy was performed after the initial rheumatic infection the number of recurrences were no less than in the rheumatic children whose tonsils were not removed.

The end-result in rheumatic disease in children did show the influence of the tonsils. The mortality in nearly 600 rheumatic children was nearly twice as high in the children whose tonsils were in at the time of the initial attack. The absence of the tonsils apparently safeguarded some of the rheumatic children against the serious cardiac complications that are usually responsible for death.

Statistical and clinical data justify the removal of the tonsils in practically every rheumatic child until other factors that influence this disease are better understood.

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DISCUSSION

DR. RUSSELL L. CECIL, NEW YORK, N. Y.—Assuming that Dr. Kaiser's statistics are correct, that a tonsillectomized child has a 35 per cent better chance against having rheumatic fever, the question arises: When, in this climate, should tonsillectomy be done? I know of no more vexing problem to mothers in New York City whose children have repeated respiratory infections without joint manifestations, but with some fever and possibly some complications in the ears. An argument generally occurs between the pediatrician, the internist, and the laryngologist. The laryngologist is disposed to advise tonsillectomy in children earlier than the pediatrician or internist. I saw a three-year-old girl just a few days ago who had repeated respiratory infections, a little fever with each attack, tonsils that look infected, and involvement of the cervical glands. The question came up whether the tonsils should be removed at once, before any serious damage was done, or whether we should wait until she was five years old. In some respects it seemed best to wait, but I think a child who is having trouble with tonsils should have them removed before serious damage to other organs is done. In children with no more than the average number of respiratory infections, it is well to postpone tonsillectomy until they are five or six. I would like to hear from Dr. Kaiser on this important point.

DR. M. J. SHAPIRO, MINNEAPOLIS, MINN.—If Dr. Kaiser has concluded that tonsillectomy should be done in 100 per cent of children who have had rheumatic fever, I wish to take issue with him. All of us have seen serious even fatal flare-ups in quiescent juvenile

rheumatic disease immediately after a tonsillectomy. A definite diagnosis of rheumatic infection in children is often difficult to establish. If all children who complain of leg pains are subjected to tonsillectomy, we will only add a good number of useless tonsillectomies to the already large number of these operations being done constantly on insufficient ground. As a result of careful study of several hundred rheumatic children for a period of twelve years, I have concluded that tonsillectomy should be done no more often in them than in any other group.

DR. KAISER (closing).—In answer to the question as to whether 100 per cent of rheumatic children should have their tonsils removed, I should say yes. That is a rather small number after all, when one realizes that in any community almost 50 per cent of children are having their tonsils removed anyhow. Private school health records show that 85 per cent have had tonsillectomies performed. The reason that so many children have tonsillectomies is that the pediatrician and the otolaryngologist advised operation for frequent colds. If one recommends tonsillectomy in all individuals in the so-called rheumatic group, it will not run over 10 per cent. Tonsillectomy is most helpful to children with tonsillitis. It is in the rheumatic group that tonsillitis occurs. If we concentrated on that group we would have fewer disappointing results.

The most definite indication for tonsillectomy in children is a history of repeated attacks of tonsillitis. That is the one infection which most students of this problem believe leads to rheumatic fever. If we restrict our tonsillectomies to children who have tonsillitis, we will not have so many failures.

DISCUSSION ON PAPER BY DR. HUGH McCULLOCH,
"INSTITUTIONAL PROVISIONS FOR THE CARE OF THE
RHEUMATIC CHILD"

W. D. STROUD, PHILADELPHIA, PA.

AT THE Children's Heart Hospital in Philadelphia, we have taken care of about 600 children with rheumatic heart disease in the past fourteen years. Three cardiologists and three pediatricians have been associated in caring for these children. We have concluded that tonsillectomized rheumatic children have done better than those seen in other clinics who have not had their tonsils removed. One of our requirements for admission to the Children's Heart Hospital is that no child will be admitted who has not had his tonsils removed. In addition to tonsillitis being an indication for removal of tonsils in the rheumatic child or in any child, we feel that a tonsillectomy should be performed earlier in children belonging to rheumatic families. Such children should be considered eligible for tonsillectomy at about the age of three years. To the parents of all these 600 children we have urged tonsillectomy for the other children in the family.

We feel that institutional care is of real benefit to children with rheumatic heart disease. The two objections I have heard raised against such institutions are these: if we put into such an institution a child who is not really rheumatic, he is exposed to the etiologic factor of rheumatic fever, through close contact with the others suffering from the disease. In the past fourteen years, we have had two epidemics apparently produced by streptococcic sore throats in nurses. Of 50 children in the institution at the time, only 12 or 14 had exacerbations of their rheumatic heart disease.

It has been argued that children of rheumatic families may, through contact with the disease, gradually develop less sensitivity to its etiologic factor. Removal to an institution and away from the family environment, might interfere with this. Since in such institutions these children are surrounded by others apparently hypersensitive to the etiologic factor, I believe such a criticism is not valid.

Points in favor of such institutions are, first, the general physical improvement which these children develop. Our hospital is within the city limits, surrounded by Fairmount Park. In such an environment, the general physical status of the children has definitely improved. They receive prolonged rest and at the same time, since a teacher is in attendance, are able to keep up with their studies and return to their own class in school after leaving the hospital. Thus, they do not suffer the introspection and inferiority complex common in children with physical handicaps, who must be associated with children much younger than themselves. One of the main objects of the institution is the education of parents. On visiting days, the head nurse lectures to parents and distributes literature of the American Heart Association. The children and parents learn the principles of hygienic care. A visiting nurse and social service workers follow this type of education in the home.

Such institutions provide graduate and undergraduate medical education, and an opportunity for clinical investigation.

For three years we have been using intravenous vaccine. The children who have received the vaccine have done no better than the control group. During a mild epidemic of reactivations, apparently produced through exposure to a streptococcic sore throat, as many of the vaccinated children developed exacerbations, as those in the control or unvaccinated group. In an effort to reduce the hypersensitivity of children to the etiologic factor in rheumatic fever, Dr. Joseph Stokes at the Children's Hospital in Philadelphia has been using a serum from whole blood of persons past the age of thirty-five in non-rheumatic families. Some children seem to have done well following this procedure.

FEVER THERAPY IN CHOREA AND IN RHEUMATIC CARDITIS WITH AND WITHOUT CHOREA*

LUCY PORTER SUTTON, M.D., AND KATHARINE G. DODGE, M.D., NEW YORK, N. Y.

FEVER INDUCED BY TYPHOID-PARATYPHOID VACCINE

DURING the past five years fever therapy has been used on the Children's Medical Service at Bellevue Hospital as the treatment of chorea. We were led to investigate this form of therapy because of the striking disappearance of a severe attack of chorea in a boy who became intoxicated by luminal and developed a high fever. A review of the literature revealed that the forms of therapy reported to have had definite effect on the duration of chorea, i.e., milk injections, nirvanol intoxication, and relapsing fever, had one factor in common, the production of fever. It had also been frequently observed that intercurrent infections had a beneficial effect on chorea. It was therefore difficult to escape the conclusion that it was the fever itself rather than the instrument which produced the fever which was beneficial in chorea.

After trying intravenous injections of typhoid vaccine with varying results, we began using typhoid-paratyphoid vaccine, with which we found we could produce fever almost at will. The reason that this vaccine was chosen as the means of producing fever was that it was cheap, easily available, reasonably safe and required no elaborate set-up or special technic. A method of procedure was developed which was given in detail in a previous publication.¹ In brief, the patient receives New York City triple typhoid vaccine (containing 1,000 million *B. Typhosus*, and 750 million each of Para A and B per c.c.) intravenously, beginning with a dose of 0.05 or 0.1 c.c., subsequent daily dosage being determined by the reaction of the patient to the previous one. The aim is to obtain a temperature of 104° to 106°. If necessary, a second dose on the same day is given. Treatment is continued daily, with occasional days of rest, until all signs of chorea have disappeared. In the mild and moderate cases this is seldom difficult to determine but in some children, particularly in those with severe chorea, where there has been marked hypotonia, it may be hard to decide just when the incoordination is due simply to weakness rather than to chorea. In these cases the child receives massage and occupational therapy. If the weakness decreases with increased activity, we feel safe in saying the attack is over. If the incoordination becomes worse, treatment is resumed. Figs. 1 and 2 show the temperature charts in two types of cases. Type 1 was a mild chorea, easy to treat, needing only small doses of vaccine to obtain the desired temperatures and responding well to a short course of vaccine. Type 2 was a severe chorea, difficult to treat, requiring a long course of treatment, and large doses of vaccine. In between these two

*From the Children's Medical Service of Bellevue Hospital and the Department of Pediatrics, New York University.

types lies the majority of the cases. The average number of treatments in the first 150 cases treated by this method was 6.24. In the mild cases the average was 5.14 treatments; in the moderate 6.47 and the severe cases 8.88. The minimum number of treatments was 3, the maximum 18.

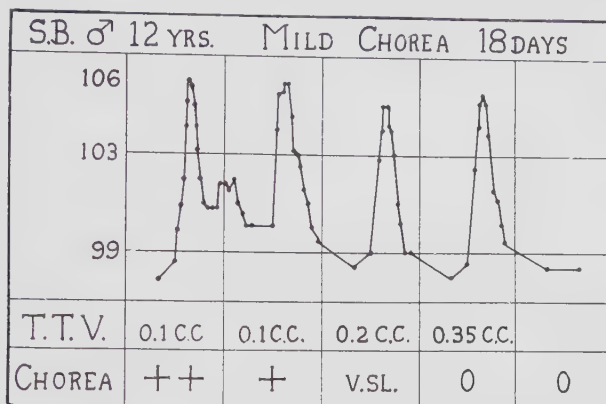


Fig. 1.

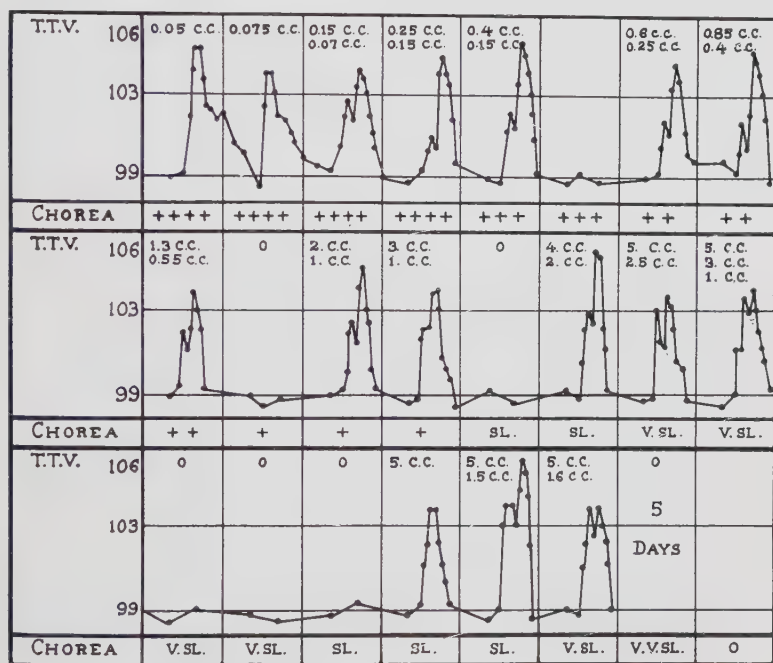


Fig. 2.

The results with fever therapy in the first 150 cases of chorea so treated have been previously reported.¹ For comparison we offered 150 cases treated on the same service before 1930 with various drugs, forms of physiotherapy and diet, plus rest in bed and isolation. Those who received fever therapy had definitely shorter attacks. The duration of chorea in the hospital in the group used for comparison, and the duration after beginning of fever treatment, are shown in Table I. This is also shown graphically in Fig. 3.

FEVER INDUCED BY RADIANT ENERGY

The disadvantages of producing fever by the intravenous injections of triple typhoid vaccine are the occurrence of protein shock, which may be very severe following the first two or three injections, and the inability to control the fever or to maintain it at the desired high level for any appreciable length of time. Investigation of other methods of producing fever led us to the conclusion that the use of radiant energy as developed by Dr. Stafford Warren and his co-workers² at the University of Rochester might prove superior to the intravenous vaccine method. We therefore had such an apparatus made, in which a patient's temperature may be raised to any desired level and maintained for as long a time as is necessary or the condition of the patient allows. Fig. 4 shows the type of temperature curve obtained by this means. Analysis of the first

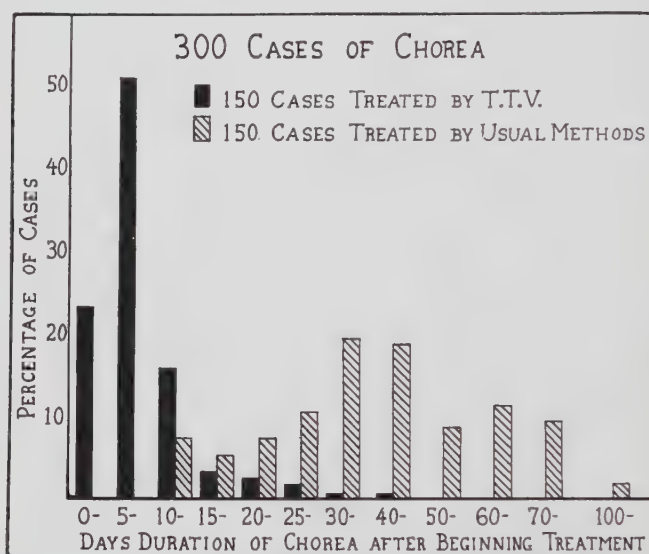


Fig. 3.

TABLE I

DURATION OF CHOREA

TYPE	NUMBER OF CASES	AVERAGE DURATION IN DAYS	RANGE IN DAYS
<i>Mild:</i>			
Comparative group	48	27.4	10- 67
Treated group	68	5.72	2- 14
<i>Moderate:</i>			
Comparative group	68	44.0	15-120
Treated group	57	8.56	3- 22
<i>Severe:</i>			
Comparative group	33	62.4	24-180
Treated group	25	15.8	5- 47
<i>Whole Series:</i>			
Comparative group	150	42.6	10-180
Treated group	150	8.5	2- 47

sixteen cases treated by this method shows that the results in terms of the duration of the chorea after one or two treatments are comparable to those obtained with a course of foreign protein induced fever (Fig. 5). Certain advantages of

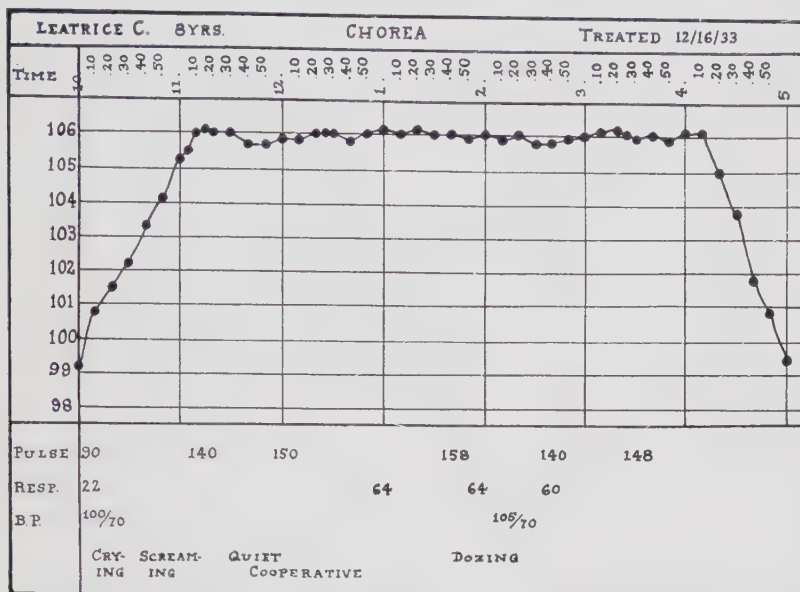


Fig. 4.

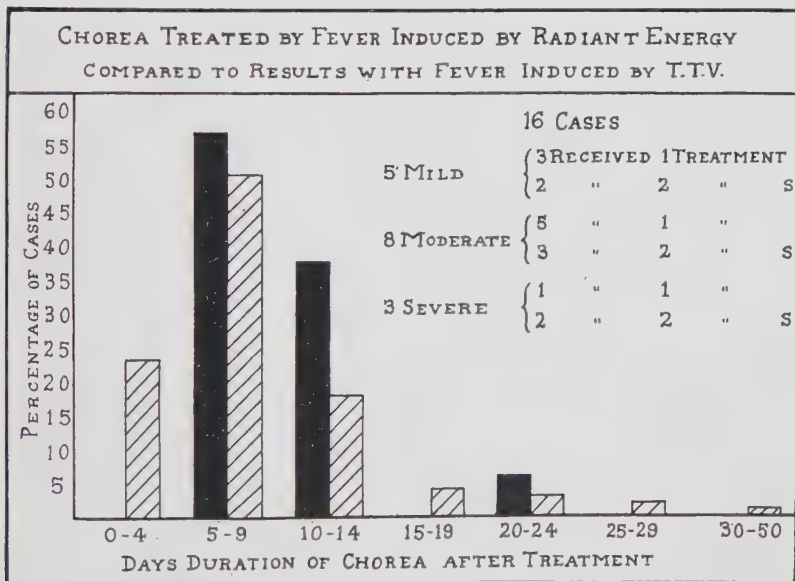


Fig. 5.—Solid black columns represent percentages of 16 patients treated by radiant energy. Cross-hatched columns represent percentages of 150 patients treated by intravenous triple typhoid vaccine.

this method may be mentioned: (1) The fever is controllable. (2) One or two treatments take the place of daily injections for a week or more of a foreign protein. (3) The patients appear distinctly less uncomfortable during treatment

with radiant energy than during treatment with foreign protein shock. (4) Except for the day of treatment the burden on the nursing staff is much diminished. The treatment of a larger number of patients may modify our results and lead us to change our opinion.

THE EFFECT OF FEVER THERAPY ON RHEUMATIC CARDITIS WITH AND WITHOUT CHOREA³

Among the first 200 patients who received typhoid-paratyphoid vaccine for chorea were 16 children with definite evidence of active rheumatic carditis at the time of treatment, and in addition 27 with clinically inactive heart disease. Among the latter group were 9 with mitral stenosis and insufficiency and 1 with both mitral insufficiency and stenosis and aortic insufficiency and stenosis. Our criteria for the diagnosis of active carditis were the presence of three or more of the following:

1. Fever
2. Tachycardia
3. Change in the quality of the heart sounds
4. Presystolic gallop sound at or just inside the apex
5. Development of new murmurs
6. Change in the quality of the murmurs present, especially the presence of a high pitched, shrill musical quality in the apical systolic murmur (sometimes described as "sea gull" quality)
7. Change in rhythm (heart-block or loss of sinus arrhythmia)
8. Electrocardiographic changes, chiefly prolongation of the P-R and QRS intervals
9. The presence of subcutaneous rheumatic nodules.

The effect of fever therapy on the clinical signs of active carditis in 5 illustrative cases is shown in Table II. In the whole group of 16, 9 had lost their clinical signs of activity by the time the chorea was over and the treatment stopped, and the remaining 7 were clinically inactive within seven to ten days after the end of the treatment. We appreciate the fact that there are cases in which the signs of active carditis subside after a short time at rest in bed, but on the other hand the tendency to chronicity of the rheumatic infection is well known.

While we did not think that the disappearance of the signs of active carditis in the majority of cases by the end of treatment was necessarily the direct result of fever therapy, we believed that it was sufficiently suggestive to justify an investigation of the effects of fever on various forms of rheumatic heart disease without chorea. Up to the present time we have treated with fever produced by radiant energy seven children with subacute rheumatic carditis without chorea, and one child with a very severe acute carditis accompanied by polyarthritis and chorea. These patients were given a fever of approximately 106° for from two to five hours at a time; five of them received two treatments each. All of these children showed decreasing signs of active infection immediately or within a comparatively short time after treatment. Figs. 6 and 7 show graphically the clinical course in the hospital of the first two patients treated by this means.

I. B. (Fig. 6) was seven and one-half years old when she was admitted in November, 1933. She had had polyarthrititis at five and six years, and is said to have had heart disease since the age of three years. The present illness began

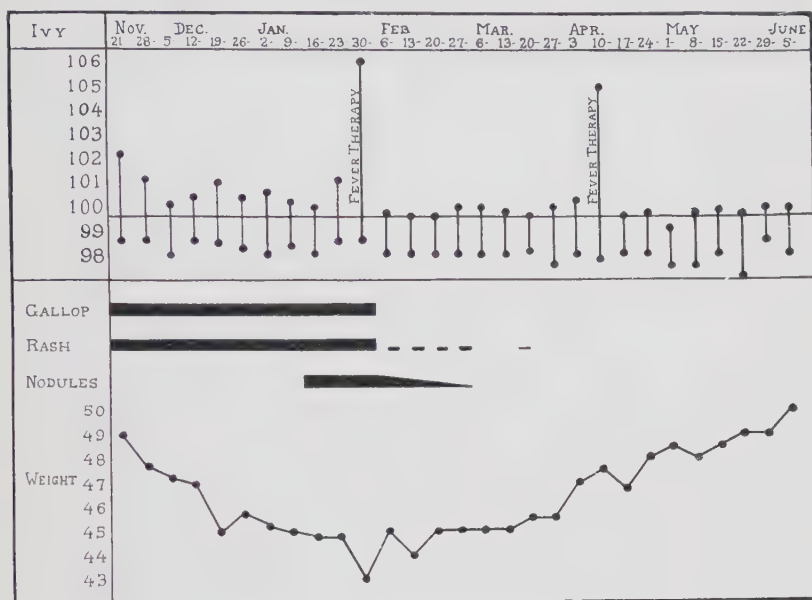


Fig. 6.

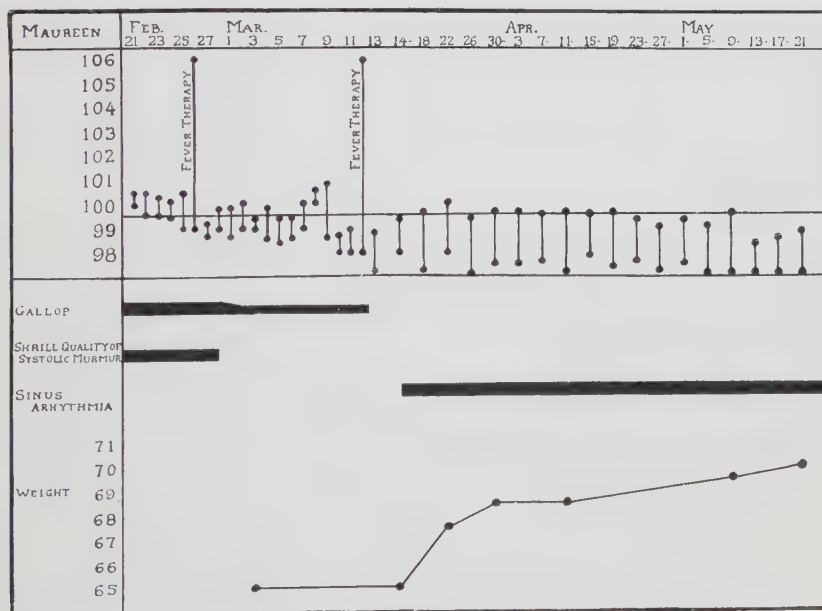


Fig. 7.

two weeks before admission with the development of an erythematous rash. Three days later she began to feel tired, to have migratory joint pains and afternoon fever. On admission she appeared acutely and chronically ill, her tempera-

ture was 101° , there was widespread erythema marginatum, her heart was enlarged, there was tachycardia, presystolic gallop, an accentuated P_2 , a loud harsh systolic murmur at the apex transmitted to the axilla and base, and a low pitched diastolic murmur. The persistence of the signs of active infection during the first ten weeks of her stay in the hospital is shown in the chart. The striking subsidence of these signs following one fever treatment of four hours between 104° and 106° is also shown. What does not show was the change in the child's general appearance and attitude. Within one week after treatment she had changed from a listless lackadaisical child with a poor appetite, to a lively, active one, bright and interested in her surroundings, and with a ravenous appetite. She was given a second treatment in the ninth week after the first, because al-

TABLE II

NO. ADM. CARDIAC DIAGNOSIS	SIGNS OF ACTIVE CARDITIS	DURATION THERAPY	DURATION OF CLIN- ICAL SIGNS OF CARDITIS	DISCHARGE DIAGNOSIS
1. a. Rheum.* b. Carditis c. S.T. d. E. & F.	Tachycardia, develop- ment of systolic and diastolic mur- murs under obser- vation	8 days	End of therapy; rate slower, murmurs softer 10 days lat- er; rate 78, S.A. present	a. Rheum. b. M.I. & S. c. S.A. d. 11a.
2. a. Rheum. b. E.H., M.I. Carditis c. S.T. d. I.	Fever on admission, tachycardia, gallop. Quality of systolic, presence of dias- tolic	8 days	End of therapy; rate 80, no gallop, S.A. present. 4 days later; diastolic mur- mur no longer heard	a. Rheum. b. E.H., M.I. c. S.A. d. I.
9. a. Rheum. b. Carditis c. S.T. d. E. & F.	Tachycardia, gallop, development of sys- tolic murmur	8 days	After 1 fever; no gal- lop, rate 100. End of therapy; rate 88, murmur less loud. 10 days later; no murmur	a. Rheum. b. -- c. S.A. d. F.
14. a. Rheum. b. Carditis c. S.T. d. E. & F.	Fever, tachycardia, gallop. Develop- ment of diastolic murmur, prolonged P-R interval	17 days	5 days after begin- ning of therapy; rate 80-90. No gal- lop. P-R interval normal before end of therapy	a. Rheum. b. -- c. S.A. d. E. & F.
16. a. Rheum. b. E.H., M.I. Carditis c. N.S.R. d. I.	Gallop, high pitched, shrill systolic. Pres- ence of diastolic	8 days	5 days after begin- ning of therapy; no gallop, systolic soft and low pitched. No diastolic heard	a. Rheum. b. E.H., M.I. c. N.S.R. d. I.

*Diagnoses were made according to the criteria for the classification and diagnosis of heart disease of the Heart Committee of the New York Tuberculosis and Health Association. Abbreviations used are: E. H., enlarged heart; M. I., mitral insufficiency; M. S., mitral stenosis; N.S.R., normal sinus rhythm; S. A., sinus arrhythmia; S. T., sinus tachycardia; E., possible heart disease; F., potential heart disease; I., functionally able to carry on normal activity; 11a, functionally able to carry on with slightly limited activity.

though her general condition continued to be good, her temperature on two occasions was above 100, and her sleeping pulse rate began to be slightly elevated. Following this her progress was steadily uphill.

M. M. (Fig. 7) was twelve years old when admitted in February, 1934. She had had repeated attacks of chorea since the age of four and one-half years, but no other rheumatic history. She had been followed by us since September, 1931, when she was treated with fever therapy for a moderate chorea. Since that

time she had had two very mild attacks of chorea. Her heart had never been enlarged but there had been an apical systolic murmur, transmitted slightly, present from the time of her first admission, and a diastolic murmur had first been heard in December, 1932. For two months previous to admission the mother had noticed tachycardia; dyspnea on climbing one flight of stairs had developed and the child had been complaining of frequent precordial pain. Two weeks before admission she had had a sore throat and had been worse since that time. On admission her temperature was 100.4° , heart rate was 130-140, there was a marked presystolic gallop, an apical systolic murmur with a high pitched shrill musical quality and a short middiastolic; no sinus arrhythmia was present. In view of the observed tachycardia and precordial pain of two months' duration, she was treated promptly without long observation in the hospital. The first treatment was for four hours at 105° to 106° , and the second, two weeks after the first, was for three hours at 106° . Following the first treatment the signs of activity decreased but they did not completely disappear until after the second. The most striking immediate change was the disappearance of the shrill musical quality of the apical systolic murmur. There was also the same change in the general appearance and behavior that was shown in the first case.

CONCLUSIONS

Fever, by whatever means produced, is a satisfactory method of treatment of chorea, in that the duration of the attacks is thereby appreciably shortened.

The presence of subacute carditis or of inactive rheumatic heart disease is not a contraindication to the use of fever therapy in treating chorea.

The subsequent uphill course of patients with subacute rheumatic carditis who received fever therapy suggests that fever may be of benefit to such patients. We believe that further investigation is warranted.

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DISCUSSION

DR. PHILIP S. HENCH, ROCHESTER, MINN.—There is a frame of mind among certain physicians that all "machine-medicine" is tinged with quackery, that even if the *deus ex machina* is a benign god, he should nevertheless be considered an unorthodox deity. Such physicians look with a suspicion, not always unjustified, upon anybody who uses machines in therapy. Fever therapy has had its origin in the laboratories of scientists of national and international repute. Its clinical utilization has so far been entrusted almost exclusively to physicians associated with large clinics and research institutions, men familiar with accurate methods for such investigations. Nevertheless, fever therapy is still enjoying its "honeymoon period" and reports thereon are still apt to be a bit enthusiastic.

The report of Drs. Sutton and Dodge is expressed in conservative terms. Their results are in general agreement with those reported at the Fifth Fever Therapy Conference in Dayton last May. Of a total of twenty-five cases of Sydenham's chorea treated by Hefke, Bierman, Schnabel, Schmidt, and Metz, about twenty cases (80 per cent) were apparently notably benefited even though several had previously not been relieved by reactions to typhoid vaccine given intravenously. A number of patients had carditis or mitral endocarditis; this was not considered a contraindication to fever therapy. Usually four or five treatments of three hours each at 105° to 106° F. were given.

At the Mayo Clinic under the clinical observation of Drs. Helmholtz and Amberg ten cases of Sydenham's chorea have been treated with fever therapy by Drs. Desjardins and Popp. The age of the patients averaged ten years (youngest seven, oldest fifteen years). The duration of infection ranged from one week to four years. From four to twelve (average six) fever sessions of three hours each were given. The patients have been observed for from six to fourteen months since treatment. One was remarkably relieved, eight were definitely benefited. One to whom inadequate fever was given was not helped. A temperature of 104° to 107° F., not lower, is advocated.

From these various preliminary experiences it seems proper to agree with Drs. Sutton and Dodge that fever therapy is a helpful and promising form of therapy for chorea.

DR. JOHN R. MOTE, BOSTON, MASS.—It seems from the results presented that patients with chorea are helped by the use of typhoid vaccine or by artificial fever. In considering such results, however, it is necessary to keep in mind that chorea is a symptom-complex and not a disease entity, the diagnosis of which is frequently difficult and not uncommonly open to question. More difficult still is the determination of cessation of the disease. This in our experience has been a repeated issue for discussion in following the clinical course of many patients. In any condition where there may be wide differences in the criteria of complete recovery the results of the use of any therapeutic agent must be open to considerable individual interpretation. Typhoid vaccine treatment has not been used on an extensive scale at the House of the Good Samaritan. In our limited experience with this therapeutic agent in this condition, we noted that in all instances the choreiform movements were definitely decreased, but unfortunately only temporarily so. In most instances they were not given quite such intensive treatment as that used by Drs. Sutton and Dodge. Since our results were neither complete nor permanent we have not felt that such severe treatment was indicated in the usual case of chorea. In the severe and exhaustive form of the disease typhoid vaccine may be an indicated form of therapy.

Dr. T. D. Jones and Dr. E. F. Bland have recently completed the analysis of a follow-up study of 1,000 consecutive chorea and rheumatic fever patients at the House of the Good Samaritan who have been followed over an average period of eight years since the onset of their disease. In this study chorea was taken as one manifestation of rheumatic fever and analyzed as such, and all other manifestations of rheumatic fever were considered other evidence of rheumatic fever. There were 482 patients who had chorea as one of the manifestations of rheumatic fever whereas 518 patients had other evidences of rheumatic fever without chorea. Of the 482 patients who exhibited chorea, 54 per cent had clinical evidence of heart damage; in contrast to this, of the 518 patients who had only other manifestations of rheumatic fever, heart damage was present in 86 per cent of the cases. When the group of 482 patients who had chorea as a manifestation of rheumatic fever is further subdivided into those who had chorea as the only manifestation of rheumatic fever, and those who had in addition to chorea other evidence of rheumatic fever, it was found that the incidence of clinically demonstrable heart disease in the former group of "pure" chorea was only 3 per cent. The latter group of patients having chorea with other evidence of rheumatic fever had an incidence of 73 per cent of heart disease, clinically detectable. Therefore, instead of being a grave manifestation of rheumatic fever, chorea in itself is seen to be a mild manifestation. And patients with chorea alone show no special predilection to heart disease unless other evidence of rheumatic fever occurs. On the other hand, any patient with chorea and with other evidence of rheumatic fever, either laboratory or clinical, should be treated as any other individual with active rheumatic fever.

A year ago Drs. Jones and Bland reported on the use of single intravenous doses of typhoid-paratyphoid vaccine in 12 rheumatic fever subjects and noted definite recurrences in six instances. If this is even an uncommon occurrence, it is a contraindication for the use of vaccine therapy where there may be evidence of rheumatic fever other than chorea.

DR. HOMER F. SWIFT, NEW YORK, N. Y.—When should fever therapy be applied in a case of rheumatic fever? In former times "hyperpyrexia rheumatica" was one of the most dreaded and fatal complications of acute rheumatic fever. It is conceivable that if this type of therapy were applied to a patient at a time when the heat regulating mechanism was very

unstable, it might place him in a state of uncontrollable hyperpyrexia, when later it might not. So many rheumatic children have evidence of low grade fever and persisting infection, that any relatively safe measure which promises aid in eliminating these symptoms should receive a thorough trial. Our own experience with fever therapy has been too limited to permit of seasoned judgment.

DR. E. STERLING NICHOL, MIAMI, FLA.—In discussing fever therapy in patients with active carditis one should differentiate between fever therapy produced with foreign protein and that induced by heat. When I was an interne on the service of Dr. Joseph L. Miller in Chicago twelve years ago, we gave intravenous typhoid vaccine to all patients with rheumatic fever *without* carditis. At that time we felt that cases with active carditis did not tolerate foreign protein therapy well. Is your experience with foreign protein in active carditis similar to that with fever therapy induced by the "hot-box"? The latter may be safer than the use of foreign protein.

DR. JOHN WYCKOFF, NEW YORK, N. Y.—This paper makes three propositions: the treatment of Sydenham's chorea with foreign protein fever, and with artificial fever, and the treatment of rheumatic carditis with artificial fever.

In our section of the country we do not feel that chorea is such a simple manifestation of rheumatic fever as Dr. Mote seems to think. The course of chorea can be tremendously shortened and the symptoms almost immediately alleviated by the use of foreign protein. As a result of such treatment chorea patients have practically disappeared from the services of the Bellevue Hospital.

With artificial fever therapy the results are even better. The temperature can be controlled. If the patients get too excited or ill the temperature can immediately be reduced. In every way it seems to be a more effective method of treatment.

We are most interested in the effects of fever therapy on patients with definite, active rheumatic carditis. The number of such cases treated by Drs. Sutton and Dodge is very small, but in practically every one of their sixteen patients, a definite change in the course of the disease is reported. Enough time has not elapsed for one to say that such cases will show fewer relapses than those which have been allowed to run the natural course of the disease.

DR. SUTTON (closing).—Though chorea seems to be the least serious of the rheumatic manifestations, it does lead eventually to cardiac damage, one reason for believing that rather heroic treatment is justified. Chorea keeps children out of school for weeks and months and is not a pleasant disease to have. Some children return asking for more treatment. They would rather have the foreign protein reaction and then be able to go back to school than to lie in bed for weeks.

In using foreign proteins we aimed for a high fever and not just for a temperature of 102°. Although we have treated 300 or 400 cases of chorea with typhoid-paratyphoid vaccine we have never noted any bad effect and never induced an attack of carditis or polyarthritis.

For the treatment of carditis we selected cases of low grade rather than acute activity. We did not treat children who had histories of congestive heart failure. We treated one acutely ill child who had chorea and also a severe acute carditis which had followed an acute polyarthritis just before her admission to the hospital. Although she was not definitely or immediately benefited by the two fever treatments she stood them well, even though during the first hour of fever her pulse rate became very rapid. Two weeks later when we gave her a second treatment she had no dyspnea and could lie flat in bed. Her pulse did not become so rapid. Now she is much better; indeed she is the picture of health.

In using hot packs for the production of fever we had one fatal result. With typhoid-paratyphoid vaccine we have had no fatality. In our first report we included the case of one child whose temperature was raised by means of a blanket pack; her temperature got out of control and went up to 109°. Clinically she had shown no evidence of activity, but at autopsy there was a definite verrucous endocarditis of the mitral valve and an old endocarditis of the aortic valve. Though the temperature was brought down she died the next day.

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